this was a significant increase ($p < 0.05$) in the incidence of adenocarcinomas of the stomach, based on the rarity of this cancer in this particular rat strain (1 in 1754, or 0.05%).

In a long-term study, Schaeffer et al.[184] investigated the effects of the PCB mixtures Clophen A30 and Clophen A60 administered to Wistar rats at doses of 100 ppm in the diet for 832 d. Hepatocellular carcinoma was found in 52 of 85 (61%) Clophen A60-exposed rats compared with only 3% in Clophen A30-treated rats and 2% in controls. The lack of carcinogenic potential of Clophen A30 may be due to its lower chlorination (40 to 42%) relative to Clophen A60 (60%).[24] However, Clophen A30 did induce altered hepatic foci and neoplastic nodules in 90% of treated rats after 800 d compared with 100% of Clophen A60-fed rats after 500 d and 36% of controls.[184]

A recent reevaluation of the liver carcinogenicity studies of PCB mixtures concluded that only the studies with the higher chlorinated mixtures, Clophen A60[184] and Aroclor 1260,[177] indicated a carcinogenic potency.[185] The design of the studies does not allow any definitive conclusions about possible sex differences in sensitivity.

As discussed previously, PCB mixtures may contain both estrogenic and antiestrogenic PCB congeners. Several studies have demonstrated antitumor or inhibitory effects on tumorigenesis by certain PCB mixtures. In one study,[177] the incidences of parafollicular cell tumors of the thyroid and granulosa theca cell tumors of the ovary were significantly lower in PCB-treated rats than in controls. Hayes et al.[186] transplanted liver nodules induced by dimethylnitrosamine (DEN) into the spleens of rats previously given DEN. Subsequent exposure to Aroclor 1254 for 24 weeks reduced transplant survival to an average of 8% compared with 21% in controls, suggesting that PCBs may inhibit nodule progression. In two studies,[187,188] Aroclor 1254 inhibited — in a dose-related manner — tumor growth in rats inoculated with a transplantable tumor. The investigators suggest that PCBs may inhibit tumor growth by altering the immune response of the host, either by increasing cellular immunity or by decreasing the production of blocking factor.

4. DDT and Its Metabolites

The carcinogenicity of DDT in experimental animals has been widely studied over the past 3 decades. In an early screening study of about 70 compounds, Innes et al.[189] first evaluated the potential carcinogenicity of *p,p'*-DDT by exposing two strains of mice to daily single doses of 46.4 mg/kg until 28 d of age, followed by a diet containing 140 mg/kg until 81 weeks of age. Hepatomas were found in male and female mice of each strain, and malignant lymphomas were observed in females of one strain.

In a five-generation study, a total of 683 mice were fed a diet containing 2.8 to 3.0 mg/kg *p,p'*-DDT and 406 mice were fed a control diet. The incidence of both leukemias and lung carcinomas was significantly elevated among the treated mice.[190] Tomatis et al.,[191] however, reported that only the incidence of liver cell tumors was significantly increased by exposure to DDT in a two-generation dose-response study in which mice were fed doses of 0 or 2, 10, 50 or 250 mg/kg technical-grade DDT (about 70% *p,p'*-DDT). In a continuation of this study,[192] the effects of the same doses of DDT were studied in six consecutive generations of mice. Exposure to all four dose levels significantly increased the incidence of hepatomas in males, whereas in females incidence increased significantly only after exposure to the highest dose. In this study, as in others,[193,194] DDT did not increase the incidence of tumors at sites other than the liver.

Cabral et al.[195] demonstrated a dose-related increase in the incidence of liver tu-

mors in rats treated with 125, 250, or 500 ppm DDT in the diet. Incidence increased from 0 of 38 in the control group, to 2 of 30 in the low-dose group, to 4 of 30 in the middle dose group, to 7 of 38 in the high-dose group. Residues of DDT, TDE, and DDE in the livers of three female high-dose rats were on average 2.5 times higher than in males.

The increase in liver tumor incidence among DDT-treated animals has been confirmed by the results of several investigations, one including mice exposed to DDT both *in utero* and after birth for life[196,197] and two reporting an elevated incidence of liver tumors after exposure to doses as low as 50 or 100 ppm in the diet.[198,199] Another study[200] demonstrated a significant increase in the incidence of malignant lymphoma among male and female mice fed 100 mg of technical-grade DDT per kilogram per day, but the study is limited by the small number of animals used. In another study[182] using technical-grade DDT (about 70% assumed to be *p,p'*-DDT), the incidence of malignant lymphoma was elevated in female, but not male, mice in a dose-response manner; however, females received time-weighted average doses four times higher than those in males. An increased incidence of hepatocellular carcinoma was found in both male and female mice fed *p,p'*-DDE (> 95% pure) in time-weighted average dietary concentrations of 148 and 261 ppm in the diet, respectively.

In contrast, no increase was reported in the incidence of tumors in rats that could be attributed to treatment with technical-grade DDT (about 70% assumed to be *p,p'*-DDT; time-weighted average concentrations of 321 and 642 ppm in the diet for male rats and 210 and 420 ppm in the diet for female rats) or *p,p'*-DDE >95% pure; time-weighted average concentrations of 437 and 839 ppm in the diet for male rats and 242 and 462 ppm in the diet for females).[182] Neither technical-grade DDT nor *p,p'*-DDE showed evidence of mammary carcinogenesis in the National Cancer Institute (NCI) rodent bioassays.[182] Two studies of DDT exposure in experimental hamsters showed no significant increase in tumor incidence in animals treated with 250, 500, or 1000 ppm in the diet.[201,202] In one of the studies, the incidence of lymphosarcomas was reduced from 50% in male controls and 41% in female controls to zero in the high-dose groups of each sex.[201]

In a two stage tumor promotion study utilizing 2-acetoamidophenanthrene as the initiating agent, *p,p'*-DDT of unknown purity in the diet at a concentration of 500 ppm (corresponding to an intake level of 25 mg/kg/d) to male Sprague-Dawley rats promoted the growth of mammary tumors.[203] No female rats were used. Only one dose level was used in the study and the tumor-promoting effect of DDT was mainly expressed as a shortened latency period to the occurrence of tumors.

However, in female Sprague-Dawley rats, 100 ppm *p,p'*-DDT in the diet decreased 7,12-dimethylbenzathracene (DMBA)-induced mammary tumor and leukemia incidence while increasing the latency period as well as animal survival.[204]

5. Mechanisms of Carcinogenicity

a. PCDDs and PCDFs

Most experimental evidence suggests that carcinogenic effects of TCDD are produced via a receptor-mediated, nongenotoxic, epigenetic mechanism.[159,171,173,205–207] Pitot et al.[208] showed TCDD to be a potent promoter of liver tumors following initiation with a single 10 mg/kg dose of DEN, with an increase in the number and volume of enzyme-altered foci and the production of well-differentiated hepatocellular carcinomas. Animals receiving only an initiating dose of DEN or those receiving TCDD alone with no initiating dose of DEN exhibited compa-

rably few enzyme-altered hepatic foci and no neoplasms. In the two-stage mouse skin assay, TCDD was only a weak initiator and inhibited the development of skin neoplasms when either DMBA or benzopyrene was applied to the skin.[209]

The maximum estimate of covalent binding of TCDD to rat liver DNA is four to six orders of magnitude lower than that of most genotoxic carcinogens.[210] Animal studies have failed to demonstrate a consistent dose response in this binding or to reproduce positive results of mutagenicity assays, lending support to the hypothesis that TCDD does not interact with genetic material.[171] Rather it promotes the activity of cells and propagates the spontaneous genetic errors already initiated by other environmental or genetic factors.

Recently, TCDD and two additional PCDD/PCDF congeners with high dioxin-like activity were evaluated for liver tumor-promoting activity, specifically the induction of altered hepatic foci (AHF), using the two-stage model of initiation-promotion.[211] 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (PeCDD) and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) as well as TCDD, acted as potent promoters of hepatocarcinogenesis in nitrosamine-initiated female rats. TCDD and PeCDD were virtually equipotent, while PeCDF displayed approximately 10% of the potency of the dioxins. These findings suggest that risk assessments must take into account the carcinogenic/promotional activity of individual congeners, as well as their potential interactive effects.[211]

Studies in several strains of mice have demonstrated that the biochemical and toxic response of TCDD is directly related to the activation of the AhR[212] which most likely results in altered expression of structural genes specifically responsible for the induction of cytochrome P4501A1.[161] Other target genes for the action of dioxin include growth regulatory genes such as plasminogen activator inhibitor-2 and interleukin-1B.[213] Many drugs and environmental chemicals, such as phenobarbital[183] and peroxisome proliferators,[214] which are potent inducers of cytochrome P450 enzymes, also induce hepatocellular carcinoma in animal studies. It remains to be elucidated whether the TCDD-AhR complex is a direct transcriptional activator for all of the genes expressed[215] and whether there is a causal link between P450 enzyme activity and carcinogenic potential of organochlorine compounds in humans.[216]

Results of recent research suggest that the P450 mediated synthesis of steroid hormones may be affected by TCDD exposure in laboratory animals.[217] Lucier et al.[218] reported that TCDD-mediated increases in liver cell proliferation and preneoplastic foci are enhanced in intact female rats compared with ovariectomized animals, suggesting that the hepatocarcinogenic actions of TCDD may themselves be dependent on ovarian hormones such as estrogens. The role of ovarian hormones in the dioxin-induced carcinogenic process is further supported by experimental findings that TCDD causes liver tumors in female rats at much lower doses than in male rats.[103]

b. PCBs

Most experimental studies provide compelling evidence that PCB mixtures and congeners are nonmutagenic, although there have been a few recent reports to the contrary. Several investigators[219,220] tested Aroclor 1254 for mutagenicity using the Salmonella mutagenicity test developed by Ames et al.,[221] and found it to be inactive. In contrast, an extensive carcinogen screening program in Japan[222] indicated that Kanechlor 300 produced chromosomal aberrations in mammalian cells *in vitro*, and that Kanechlor 500 induced chromosomal aberrations in mouse bone marrow cells after *in vivo* PCB administration. However, both PCB mixtures showed no genotoxicity in five additional

tests, and results of this study are limited by the fact that no dose data were given. Sina et al.[223] found that doses of 0.3 to 3m*M* Aroclor 1254 produced DNA damage in a dose-related manner in a rat hepatocyte assay used to measure DNA single-strand breaks induced by xenobiotics, and Sargent et al.[224] observed chromosome breakage, rearrangements, and mitotic delay in human lymphocytes incubated *in vitro* with 0.011 to 1.1 μg/ml Aroclor 1254. Despite strong evidence against the mutagenicity of PCBs, few of the 209 possible PCB congeners have been tested individually for mutagenicity and it remains possible that they interact with genetic material through the ability of some congeners to be metabolized to arene oxide intermediates or other reactive species.[24]

In contrast to this lack of genotoxic and/or tumor-initiating potential, PCBs have been found to be efficacious tumor promoters in mice and rats when administered for extended periods of time following an initiating agent. In 1973, Ito et al.[174] demonstrated an enhancement of nodular hyperplasia and hepatocellular carcinoma by PCBs when they were coadministered in the diet with the established carcinogen BHC. Since then, extensive studies have provided evidence of the promoting effects of PCBs using two-stage carcinogenesis models with various initiating agents. As with TCDD, extended PCB exposure has been reported to promote the induction of liver tumors initiated by DEN[225-227] and by *N*-2-fluorenylacetamide.[228] A study by Kimura et al.[229] showed that only when PCBs were given after, but not before or together with, the initiating agent 3′-methyl-4-dimethylaminoazobenzene did they induce hepatic tumors in rats. There is also evidence suggesting that promotion by Aroclor 1254 can occur in the lungs of infant mice after dosage with an initiator.[230]

The PCB congeners that most actively promote hepatic tumors (3,3′,4,4′-TeCB and 2,3,4,4′,5-PeCB) have been shown to also be the most potent inducers of liver enzymes such as cytochrome P450-dependent monooxygenases.[24,227] More detailed studies of the possible interactions between halogenated biphenyls and endocrine systems in animals are necessary before reaching any conclusions about the mode of action or the time course of responses to these chemicals in humans.

c. DDT and Its Metabolites

DDT and its structural analogs are all reported to be nonmutagenic.[49,155] Many studies have demonstrated the tumor-promoting activity of DDT in rodent livers without concomitant increase in tumor incidence in other organs.[231-233] The results of one study[205] suggest that DDT may accelerate the development of mammary gland tumors initiated in the male rat by 2-acetamidophenanthrene. No mammary gland tumors were found in rats treated with DDT alone. Given that the apparent promoting effect of DDT was seen in the male rat, and that no evidence of mammary carcinogenesis was seen in female rats and mice fed technical-grade DDT or *p,p′*-DDE,[182] the relevance of this finding to breast cancer in women is questionable.

The molecular mechanism by which DDT and related compounds act as tumor promoters has not been conclusively established. Trosko and Chang[234] have reported an apparent correlation between drug-induced inhibition of intercellular communication *in vitro* and promotion of tumor development *in vivo*. Flodström et al.[207] in support of this hypothesis, found that DDT and three structural analogs (bromopropylate, chlorobenzilate, and dicofol), which did inhibit cell-cell communication, also significantly enhanced the development of altered hepatic foci in male rats. In contrast, fenarimol, the DDT analog tested that did not affect junctional communication, also did not act as a potent tumor promoter. Several reports have

confirmed an association between impaired intercellular communication and the promotion step of carcinogenesis.[235,236]

Flodström et al.[207] reported no strict correlation between CYP2B induction/liver growth and tumor promotion-related effects *in vivo* and *in vitro* for DDT and four structural analogs, suggesting that they may not be appropriate qualitative markers of liver tumor-promoting activity.

III. EPIDEMIOLOGICAL DATA

A. Organochlorines and Breast Cancer

1. Evidence from Temporal and Ecological Studies

As a methodological approach to assessing relationships between risk factors and disease, ecological studies have well-known limitations, most of which stem from the absence of exposure information for individual cases, the cross-sectional nature of many ecological studies, and the use of aggregate discase rates. Because variations in cancer incidence can be linked to virtually any parallel shift in lifestyle or environmental exposure, ecological or temporal analyses may result in fallacious conclusions. Even when a putative exposure is thoughtfully selected for evaluation, an observed effect may be due to an unassessed covariate. Control of such covariates is difficult in ecological studies, and especially so if covariates differ across time and geography.[237]

Ecological and temporal evaluations of the relationship between breast cancer and organochlorine exposure face additional challenges. Measures of organochlorine levels vary substantially with methods of population sampling, specimen source, laboratory technique, and method of reporting. In addition, various chemicals with different (or opposing) estrogenic effects have been introduced and withdrawn over concurrent or overlapping periods of time. Thus, populations are exposed to complex mixtures of organochlorine chemicals with varying or opposing estrogenicity, making it difficult to examine particular chemicals in relation to specific diseases. Problems also attend the use of cancer rates in ecological or temporal analyses. In general, an evaluation of a relationship between cancer rates and a possible causal factor is complicated by a (variable or unknown) latency between exposure and tumor diagnosis, and by possible age-specific exposure effects. With few exceptions, cancer incidence rates were not reported during the decades prior to the use of these selected organochlorines, precluding comparisons of rates before and after the introduction of these organochlorines. Evaluations based on mortality rates have their own limitations, as mortality rates may be affected by changes in survival and diagnostic classification.

Given the relatively recent introduction of these organochlorines, and a presumed latency between exposure to a causal agent and breast cancer development, it is most practical to examine possible parallels between breast cancer incidence and the patterns of the use of DDT, a putative estrogenic agent that was also one of the earliest and most extensively used organochlorine pesticides.

Within the U.S., time trends in breast cancer incidence do not provide substantial evidence of a relationship with DDT exposure. The last 2 decades have witnessed modest increases in the incidence of breast cancer among younger women (<40 years of age).[238] These gradual increments do not parallel the introduction, extensive use, and subsequent withdrawal of DDT. Although dramatic shifts in U.S. breast cancer incidence rates have been observed among older women during the last few decades, these changes have been attributed, to a large extent, to heightened public awareness and use

of screening mammography.[239,240] For example, a brief perturbation of rates during the late 1970s probably reflects increased mammographic screening following the announcements of breast cancer diagnoses in two prominent American women, Happy Rockefeller and Betty Ford, and to subsequent increases in mammographic screening.[238] Steep increases in breast cancer rates between 1982 and 1986 were seen predominantly among age groups with greater mammographic utilization,[238] and were due largely to increases in early or *in situ* tumors. The stabilization (and slight decline) in breast cancer incidence rates observed between 1987 and 1989 followed this period of steep increases, and may reflect saturation of mammographic screening and a diminished pool of prevalent cases.[239,241]

One broad international observation is noteworthy. Although high tissue levels of some organochlorines have been reported from Japan, breast cancer incidence rates in that country are still low relative to those of other industrialized nations, including the U.S.[242] Moreover, the rate of increase of breast cancer incidence sharply accelerates when Japanese women migrate to the U.S.[243] This dramatically increased risk is attributed to lifestyle changes (e.g., diet) and would not be observed if breast cancer rates were largely driven by organochlorine exposure.

Finally, ecological evaluations of racial and socioeconomic data are not consistent with a relationship between organochlorine exposure and breast cancer rates. The body burdens of DDT are higher among blacks, relative to whites,[5,45] whereas whites have overall higher rates of breast cancer[242,244] DDT exposure has also been associated with lower socioeconomic status, whereas breast cancer[245] rates are elevated among higher socioeconomic groups.[44]

To date, three published ecological studies have evaluated the relationship between exposure to selected organochlorine chemicals and breast cancer.[246–250] The first study evaluated disease outcomes in a residential population exposed to dioxin after an industrial accident in Seveso, Italy, in 1976.[246,247] The study population included persons who had ever lived in the contaminated area and who were 20 to 74 years of age during the 1976 to 1986 follow-up period. Population exposure was classified according to soil contamination levels in three geographical zones (A, B, and R) variably affected by the accident. The original analysis evaluated mortality outcomes; an evaluation of breast cancer was impeded by small numbers of cases, particularly in the most highly contaminated zone A.[246] More recently, the investigators compared cancer incidence rates in the exposed and an unexposed reference population.[247] In areas A and B (highly and intermediately contaminated zones, respectively), there was a deficit of breast cancer (11 observed vs. 16.3 expected), but the interpretation is limited by small numbers. In zone R, an area with lower and uneven dioxin contamination, breast cancer incidence did not differ markedly from the reference rate. These findings are compatible with, but not overwhelmingly supportive of, laboratory evidence of a reduced incidence of hormone-dependent tumors of the mammary gland among female rats exposed to TCDD.[103]

The lower breast cancer mortality rates observed in Israel in 1986 than in 1976 has been attributed to marked decreases in specific organochlorine pesticides (DDT, α-HCH and γ-HCH) in breast milk, noted in 1980, and in cow's milk, documented in 1978.[248] However, evidence for such a link is not compelling. If a latency between exposure and diagnosis is also taken into account, it is highly unlikely that the decreased breast cancer incidence observed in 1986 can be attributed to declining organochlorine exposures during the 1970s. Because excess mortality continues for a decade or longer following primary treatment, a substantial proportion of the breast cancer deaths

occurring in 1986 must have been diagnosed prior to or concurrently with the decline in these organochlorine levels posing a serious challenge to the proposed interpretation. An alternative explanation may be considered. Breast cancer incidence rates differ substantially among the various ethnic groups in Israel.[242,244,251] Recent decreases in Israeli breast cancer mortality rates could be due to temporal changes in migration patterns and consequent shifts in the ethnic composition of the population, that is an early influx of high-risk Western women,[242] and later immigration of low-risk Asian and African women.[252] Moreover, as discussed by Shames et al.,[253] the Westin and Richter[248] breast cancer mortality figures are based on the single years 1976 and 1986. An examination of the data for the 5 year periods around 1976 and 1986 actually reveals a 10% decline in the breast cancer mortality rate, substantially less than the 22% decrease reported by Westin and Richter.[248]

A recent report by the New York State Department of Health[249,250] describes results of an investigation that used a design with ecological elements and case-control structure to evaluate the relationship between breast cancer incidence and exposure to air pollution in Long Island (NY). Cases and controls were 20 to 79 years of age, and had lived on Long Island for at least 20 consecutive years prior to diagnosis (or study interview). Breast cancer cases were identified between 1984 and 1986, and matched to controls by age and county (Nassau or Suffolk). An index of exposure to air pollution was based on residential proximity (using a square kilometer grid system) to a chemical or industrial manufacturing facility, or to a high motor vehicle traffic area. Information concerning specific industrial air pollutants was not available. The results of this study did not support a relationship between air pollution overall and premenopausal breast cancer. In addition, there was no evidence of an effect of industrial or motor vehicle traffic air pollution on breast cancer risk. However, a statistically significant increase in postmenopausal breast cancer risk was observed in Nassau County among women who had lived near chemical facilities. It is not clear whether factors with confounding potential, such as ethnic group, social class, or alcohol intake, were accounted for in the analysis. Despite some methodological limitations, the possibility that risk of postmenopausal breast cancer is increased by some pollutants arising from chemical plants[250] warrants further investigation. The study also evaluated a potential link between residential use of termiticides, specifically chlordane, and breast cancer. No consistent elevation in breast cancer risk was observed among women reporting termiticide application at home; however, direct exposure measurements were not available and recall of termiticide use in general, and chlordane application in particular, was likely to be unreliable.

2. Evidence from Occupational Studies

Relative to the general population, exposures to organochlorines are substantially higher among workers who have direct contact with these chemicals. Occupational exposure to organochlorines has been most extensively evaluated for soft tissue sarcoma and non-Hodgkins lymphoma after exposure to phenoxyacetic acids and their contaminants.[254-260] The estrogenic properties of some organochlorines have led to speculation that these chemicals may also be related to risk of human breast cancer,[250,261-267] but to date, only a few published studies have evaluated breast cancer risk among women occupationally exposed to organochlorine chemicals. Three cohorts of women exposed to phenoxy herbicides have been evaluated for breast cancer risk,[268-272] whereas four studies — two published[273,274] and two unpub-

lished[275] (Sinks 1994, personal communication) — have provided estimates of breast cancer risk among women exposed to PCBs. Further occupational studies on associations between exposure to the organochlorine compounds covered in this review and breast cancer have not been found.

Lynge[268] evaluated breast cancer incidence among 1069 women ever employed before 1982 in the chlorophenoxy herbicide industry in Denmark. The largest of the Danish facilities included in this study began manufacturing phenoxy herbicides in 1947, but for most plants, production began during the 1950s or 1960s. Employee exposure levels were not known, but dioxin (TCDD) exposure was presumed to have occurred because the herbicides were contaminated with this chemical The original study evaluated cases arising during 18,000 woman-years at risk from 1947 through 1982. Linkage to the Danish National Cancer Registry was used to identify cases, and national rates were used to compute expected numbers of cases. Excellent (99%) follow-up was achieved. A total of 13 women were diagnosed with breast cancer, providing a standardized incidence ratio SIR of 93. Further follow-up (1983 to 1987) of the herbicide workers did not include evaluation of breast cancer risk.[276]

Manz et al.[269] published data regarding the cancer mortality experience of 399 women who were employed for at least 3 months from 1952 through 1984 at a German herbicide plant where dioxin (TCDD) exposures were presumed to be high. Manufacture of the herbicides began in 1951. Although the TCDD body burdens of cohort members is unknown, a nonrandom survey conducted in 1985 (after the plant had closed) showed median TCDD adipose tissue levels of 60 to 137 ppt across exposure subgroups; these levels were substantially higher than general population background levels of 7 to 20 ppt. Relative to German national rates, the overall cancer mortality rate among women was lower than expected, but a marginally significant standardized mortality ratio (SMR) of 215 was observed for breast cancer (based on nine deaths). A later report focused on deaths occurring among the female workers, and included as a second reference group women who had been employed as gas workers for at least 10 years.[265] With one additional breast cancer death, the SMR increased to 237 (and attained statistical significance). When compared with gas workers, the relative risk of breast cancer among herbicide workers was 208. Higher risks with increased duration of employment were noted for specific industrial departments, but the confidence intervals (CI) were wide. The age distribution of the workers was not reported, but eight of ten breast cancer deaths occurred among women less than 55 years of age, implying premenopausal diagnoses.

Breast cancer mortality was also evaluated among 1527 female workers identified in 11 occupational cohorts from seven countries.[270] The earliest employment was in 1955 (four cohorts) but three cohorts experienced first exposure at least 15 years later. For all but two of the cohorts, those who were "ever employed" in the phenoxy herbicide industry were eligible for study participation. Workers were classified according to the likelihood of phenoxy herbicide exposure based on job history. Mortality was ascertained through national records or by active follow-up; 95% of the population was successfully followed. Expected numbers of cancer deaths were based on national rates. The analyses included separate evaluations of male (SMR = 345, based on two observed deaths) and female breast cancer (SMR = 30, based on one observed death) in the subgroup with known phenoxy herbicide exposure. A subsequent reanalysis included both incidence and mortality data, and focused on the subgroup of 701 women (10,782 person-years) with known exposure to phenoxy herbicides.[272] Overall, breast cancer incidence

was not elevated in this cohort (SIR = 91), although there was a slight increase of risk within the first 10 years of exposure (SIR = 143). Breast cancer mortality ratio (SMR = 30) was unchanged from the earlier report. Due to small numbers, site-specific analyses were not conducted in a further subgroup of women with probable TCDD exposure.

Brown[273] examined the cancer mortality experience of 1318 women employed in the heaviest PCB exposure areas of three electrical capacitor manufacturing plants (two in New York, one in Massachusetts). Capacitor manufacturing in these factories had begun in 1938 and in 1946; 30,492 woman-years of risk were accrued through 1981. Surveys conducted at the New York plants confirmed high contamination among workers employed in similar jobs. The first of these surveys (1976) revealed extremely high mean serum levels of 84 and 1470 ppb for particular PCB mixtures (Aroclor 1254 and 1242, respectively). The second survey conducted in 1979 (subsequent to discontinued PCB use) showed that mean PCB serum levels had decreased to 54 and 277 ppb for the same chemicals (but were still about substantially higher than of the U.S. general population). For breast cancer, a standardized mortality ratio of 77 was observed, based on nine deaths.

Sinks et al.[276] assessed outcomes (1957 to 1986) among 846 female employees who had been exposed to PCBs at an electrical capacitor plant. Although breast cancer mortality was not addressed in this report, a subsequent analysis (Sinks, 1994, personal communication) provided a SMR of 51 (based on two breast cancer deaths). Two additional unpublished evaluations of breast cancer risk are also available. Breast cancer mortality was not assessed in a published follow-up study (1946 to 1982) of 1556 female workers employed at an electrical capacitor plant;[277] however, a later report to the Ontario Board of Workmen's Compensation[274] indicated that two breast cancer deaths had occurred in this cohort (vs. 1.99 expected). Also included in the Ontario report is a small cohort of 521 women employed at one of the electrical capacitor plants studied by Brown[273] but not included in Brown's analysis. SMRs were not computed in this report, but can be calculated as 133 for breast cancer (five deaths observed).

In the aggregate, these reports do not support a relationship between breast cancer and occupational exposure to PCBs. The results of the phenoxy herbicide studies are less consistent; one study supports an association,[269] whereas the others do not.[268,270,272] The evaluation of breast cancer risk in occupational cohorts is frustrated by many factors, including the relatively limited numbers of women working in the chemical industry during the decades in question, and the small numbers of breast cancer cases arising in the cohorts. In addition, the actual exposure of cohort members is unknown. Quantification of occupational organochlorine exposures has been sporadic, and the absence of individual exposure measures (by way of adipose tissue or serum sampling) is a limitation of all the organochlorine-exposed occupational cohorts. The level of exposure may be even less certain for female employees (except for the capacity workers), who were presumably likely to work in less-contaminated office areas during the decades in question. The choice of an appropriate set of rates with which the SMRs are computed adds a further element of difficulty, because employed populations have, at enrollment, lower mortality and disease occurrence rates than the general population.[278]

In summary, these studies share several limitations, and the results are hardly conclusive. Many of these limitations would tend to result in an underestimate of the association between the studied organochlorines and cancer but it is unlikely that a strong relationship would have been missed if one actually did exist.

3. Evidence from Case-Control Studies

Several case-control studies conducted since the late 1970s have raised the issue that women exposed to the chemicals DDT or PCBs may have higher rates of breast cancer than women not exposed to those chemicals. Wasserman et al[261] reported higher concentrations of *p,p'*-DDT, *o,p'*-DDT, and PCBs in extracted lipids of malignant breast tissue when compared with adjacent apparently normal mammary and adipose tissues. However, as the authors themselves note, the data in this study are based on only a few cases and are therefore "inadequate for conclusions regarding the amount of the organochlorine compounds in cancer patients." A recent pilot study[264] found that mean concentrations of PCBs and *p,p'*-DDE were 50 to 60% higher in breast tissues of 20 women who had breast cancer than in controls.

Canadian investigators[266] recently measured fat and plasma concentrations of HCB, DDE, and 10 PCB congeners in a small sample of breast cancer patients and controls with benign breast disease, taking into account the estrogen receptor (ER) status of primary tumors. Mean adipose tissue concentrations of organochlorines in ER-negative cases were lower than those of controls. However, ER-positive cases had substantially higher DDE fat and plasma concentrations, suggesting that women with hormone responsive breast cancer may have a higher body burden of DDE when compared with controls.

Other epidemiological studies failed to support an association between organochlorine compounds and breast cancer. In a small Danish study,[262] PCB and DDE levels in the adipose tissue of deceased breast cancer patients and in the biopsy material from newly diagnosed breast cancer patients were not significantly different from those in deceased controls and in noncancer patients, respectively. This suggests that the occurrence of breast cancer does not relate to the accumulation of PCBs and DDT in breast adipose tissue. A similar finding was reported by Mussalo-Rauhamaa et al.,[263] who found no statistically significant differences between breast cancer patients and controls in residue levels of *p,p'*-DDT, *p,p'*-DDE, *o,p'*-DDD, HCB, heptachlorepoxide, or PCBs in breast adipose tissue. They did observe a difference in the frequency of residues of β-HCH, but this may have been a chance finding among the several comparisons made. The primary limitations of the above studies are their small size and the failure to control for possible confounding by several established breast cancer risk factors.

The two largest studies so far to evaluate the association between organochlorine compounds and breast cancer have produced inconsistent results.[265,267] Wolff et al.[265] analyzed PCB and *p,p'*-DDE concentrations in sera from stored blood specimens of 58 cases and 171 controls sampled from 14,290 women enrolled in the New York University Women's Health Study, a prospective study designed to examine the effects of endogenous estrogen levels on breast cancer risk.[279] The authors reported that mean levels of *p,p'*-DDE were significantly higher (by 35%, or 2.7 ng/ml) for breast cancer cases than for matched control subjects. Mean levels of PCBs were 15% higher ~~in~~ cases than in controls, but the difference was not statistically significant. An elevation of serum *p,p'*-DDE concentrations from 2.0 ng/ml (10th percentile) to 19.1 ng/ml (90th percentile) was associated with a substantial increase in the risk of breast cancer (odds ratio [OR] = 3.68, 95% CI 1.01 to 13.50); alternatively, there was a statistically significant 9% increase in the risk of breast cancer per ng/ml increase in *p,p'*-DDE when serum *p,p'*-DDE was examined as a continuous factor. The odds ratio per ng/ml change in PCB concentration was 1.08 and not statistically significant, corresponding to less than a twofold risk for an elevation of levels of serum PCBs from

3.9 ng/ml (10th percentile) to 10.6 ng/ml (90th percentile) (OR = 1.70, 95% CI 0.79 to 3.68). This nonsignificant association was further reduced after adjustment for *p,p'*-DDE. These estimates were all adjusted for several potential confounders, including family history of breast cancer, lifetime lactation, and age at first full-term pregnancy.

The study by Krieger et al.[267] was a case-control study nested in the Kaiser Permanente Medical Care Program multiphasic health examination cohort of 57,040 women in the San Francisco Bay area. The study population was a random sample of 50 breast cancer cases from each of three ethnic groups (Caucasian, African-American, and Asian) and equal numbers of individually matched controls, all of whom had blood samples stored in the late 1960s, independent of concern about risk of breast cancer, and were followed up through 1990. Among all racial/ethnic groups combined, women with breast cancer and their matched controls did not differ significantly in their mean serum levels of either *p,p'*-DDE or PCBs. For cases and controls, respectively, mean *p,p'*-DDE levels were 43.3 and 43.1 ppb and mean PCB levels were 4.4 and 4.8 ppb. The authors concluded that the results of the study did not lend support to the hypothesis that higher serum levels of *p,p'*-DDE or PCBs increase the risk for breast cancer. However, serum levels of *p,p'*-DDE did show a positive, albeit statistically nonsignificant, association with breast cancer among Caucasian and African-American women but not among Asian women. The data appear to be consistent with a threefold increase in risk among Caucasian women with the highest levels of *p,p'*-DDE exposure. These subgroup analyses, however, do not carry the same statistical force as the overall result.

4. Summary Analyses

We have undertaken analyses to obtain a summary SMR or SIR for occupational cohort studies, a summary ratio of mean concentrations for case-control studies, and a summary OR for case-control studies that reported this effect estimate.[280]

To arrive at the summary estimates, we did not apply any selection criteria other than the availability of data in the published studies. The studies were not judged as to their validity. For the purpose of comparability, whenever available the results for *p,p'*-DDE in adipose tissue were taken from studies that evaluated more than one compound related to DDT and its metabolites.

a. Occupational Studies

For occupational cohort studies, the observed and expected number of breast cancer cases were obtained first for each study. The summary estimate was then calculated as the ratio between the sum of the observed numbers of cases and that of the expected numbers. The aggregated estimate was therefore weighted proportionally to the size of the cohort and its rate of breast cancer. The 95% CI for the summary observed-to-expected ratio (O/E ratio) was obtained based on a Poisson distribution.[281] This O/E ratio can be interpreted as a relative risk estimate.

Three cohorts with possible occupational exposure to TCDD were discussed in a preceding section (see "Evidence from Occupational Studies").[268-270] Kogevinas et al.[272] reported additional incidence experience among a subset of women from the study by Saracci et al.[270] who reported the mortality experience. Observed and expected cases were not counted twice in these analyses, but it is assumed that exposed and nonexposed cases with breast cancer have similar fatality rates.

There were a total of 34 observed cases of breast cancer, yielding a summary O/E ratio of 1.04 (95% CI 0.72 to 1.45). Excluding women who were judged to be nonexposed to TCDD in Saracci et al.[270] (four

observed cases) and those whose TCDD exposure was judged to be unlikely in Kogevinas et al.[272] (six cases), the summary O/E ratio was 1.08 (0.68 to 1.58). CI estimates in both instances were wide and included the null value of 1.0.

Similarly, four studies reviewed in "Evidence from Occupational Studies" have evaluated breast cancer risk among female workers occupationally exposed to PCBs.[273–275] There were a total of 18 observed cases of breast cancer, yielding a summary O/E ratio of 0.84 (95% CI 0.50 to 1.33).

b. Case-Control Studies with Ratio of Mean Concentrations as the Effect Measure

For case-control studies, the summary ratios of the mean concentrations of the studied organochlorines between cases and controls were derived from the weighted averages of the logarithm of the ratios from the individual studies. Weights were taken to be proportional to the inversed variances of the log ratios of the mean concentrations.

A summary analysis on the ratio of mean concentrations has been performed by Key and Reeves.[282] We undertook a similar analysis, but we have included data from Wasserman et al.[261] for the DDE analysis, data for deceased cases and controls from Unger et al.[262] for the PCB analysis, and data on wet weight basis from Falck et al.[264] for both compounds.

We obtained essentially the same results as those obtained by Key and Reeves[282]: for DDE the summary ratio was 1.08 (95% CI 0.98 to 1.19) and for PCB it was 1.03 (0.96 to 1.10).

c. Case-Control Studies with OR as the Effect Measure

For case-control studies that provided an OR ratio as an effect estimate, the summary OR estimate was derived from the weighted average of the logarithm of ORs from individual studies. Weight was taken to be proportional to the inverse variance of the log OR. For studies that did not provide the log OR and its variance, the variance was derived from the reported CI estimate. We calculated the 95% CI of the summary OR by taking the inverse sum of weights as the variance of the log summary OR.

Wolff et al.[265] and Krieger et al.[267] measured *p,p'*-DDE and PCB in serum samples. In addition to the mean concentrations for breast cancer cases and for controls, they provided an estimated OR associated with each unit (ppb) increase in exposure to PCB. Because the unit is small, to avoid greater rounding errors in calculating the variance from the CI presented in Kreiger et al.,[267] individual OR estimates for each ethnic group, rather than that for the total group, were used. The summary OR was near the null value for PCB, that is 1.02 (0.94 to 1.11).

For *p,p'*-DDE, it is difficult to do a straightforward summary analysis of data presented by Wolff et al.[265] and Krieger et al.[267] This is because the exposure information for Krieger et al.[267] refers to the time period 1964 to 1971 when levels were much higher; the exposure data in Wolff et al.[265] refer to the time period 1985 to 1991 when *p,p'*-DDE levels were substantially lower following the ban of these compounds in 1972.[6]

By assuming that the range of exposure in the population studied by Wolff et al.,[265] if backdated to 14 years ago as in the Krieger et al.[267] study, would be similar to that noted for Caucasians in Krieger et al.,[267] we may roughly approximate that in the Wolff et al.[265] study the OR per standard deviation (SD) would be exp (22.8 ppb*0.0823 per ppb) = 6.53. Accordingly, the combined OR per SD and their 95% CIs were calculated. The summary OR was 1.27 for *p,p'*-DDE (95% CI 0.95 to 1.69) with statistically significant heterogeneity among the four groups

(X^2 with 3 d.f = 9.98; $p = 0.02$). This heterogeneity is accounted for by the heterogeneity between Wolff et al.[265] and Krieger et al.[267]

5. Methodological Discussion

The majority of the above-mentioned studies[261-264,266] cannot be easily interpreted, mostly because of their small sample size and their failure to adequately control for known breast cancer risk factors. Some of the studies had fewer than 20 breast cancer cases,[261,262,264,266] thereby limiting their ability to generate precise estimates of the association, if any, between these organochlorines and breast cancer. Also, in several investigations, the study population was not clearly defined, raising uncertainty as to whether the selected controls were representative of the study base. Therefore, most of the reliable evidence derives from the two nested case-control studies.[265,267]

As previously discussed, it is postulated that through their weak estrogenic properties, organochlorines such as *o,p'*-DDT and *o,p'*-DDE may increase the risk of breast cancer. Evidence implicating other sources of exogenous estrogens, such as oral contraceptives[283] and postmenopausal hormone replacement,[284] in breast cancer is inconsistent, and an association between exogenous hormone use and organochlorine exposure is unlikely. Oral contraceptive use and hormone replacement therapy are therefore unlikely to be confounders of the association between organochlorines and breast cancer However, an association between organochlorines and breast cancer would be difficult to detect in the presence of the generally large doses of exogenous estrogens relative to the small daily doses estimated for human exposure to organochlorines.[284]

Women in the study by Krieger et al.[267] were enrolled prior to the federal restrictions on the use of DDT, which, together with differences in geography and socioeconomic status, most likely accounts for the fact that mean *p,p'*-DDE levels were four to five times higher in this study than in the study by Wolff et al.[265]

MacMahon[286] has suggested that it is unlikely that an association between DDT or its metabolites and breast cancer would be seen in women whose samples were taken within 6 months of diagnosis but not in women whose sera were sampled many years earlier; that is, closer to the postulated induction time of breast cancer. Moreover, high adipose levels of *p,p'*-DDE 20 years before diagnosis would most likely be reflected at the time of breast cancer development, and no relationship was found between breast cancer risk and *p,p'*-DDE levels in the study by Krieger et al.[267] even among the 14 women whose sera were collected less than 5 years prior to diagnosis.

The most likely explanation for the inconclusive epidemiological findings regarding the association between organochlorines and breast cancer is that these compounds, at the levels they are currently encountered, are too weak to show any effect, although a balance between estrogenic and antiestrogenic responses to individual compounds cannot be excluded. For example, the biological activity and toxicity of both PCBs and PCDDs are known to be specific to the structure and/or degree of chlorination of the individual congener. Only 60 to 70 of the possible 209 PCB congeners have been identified in humans, and the 20 congeners that represent the total value that is commonly reported in epidemiological studies include both estrogenic and antiestrogenic compounds.[287]

The complex epidemiology of breast cancer, extensively reviewed elsewhere by others[288] and Lipworth,[289] is discussed in more detail in the context of organochlorines in an accompanying paper with an epidemiological focus.[280] Most established risk factors for breast cancer are related to the woman's reproductive life[288] and thus are likely indicators of endogenous hormones. However, the associations, for ex-

ample, of parity, age at first birth, age at menarche, age at menopause with breast cancer risk,[290] are weak for the most part. There is also emerging evidence that hormonal effects on the breast epithelium are complex, operate probably from intrauterine to adult life, and depend on number of cells at risk, cellular replication, and terminal differentiation.[291] Although there are several established associations between indicators of endogenous hormones and risk of breast cancer in women, the role of potent exogenous hormones such as oral contraceptives and hormone replacement in menopause is still controversial despite considerable epidemiological effort.[290,292]

B. Organochlorines and Endometrial Cancer

1. Evidence from Temporal and Ecological Studies

The etiology of malignant endometrial cancer has been most closely tied to estrogens. Estrogenic exposures — most notably postmenopausal obesity and unopposed menopausal estrogen therapy — have consistently been associated with an increased risk of this tumor. For menopausal estrogens, the relative risk estimate is five or higher among long-term users.[293,294] In comparison, for breast cancer, the increase in risk is minimal.[295] Postmenopausal obesity — a trait strongly associated with estrogen levels — is also more strongly related to endometrial cancer than to breast cancer.[293] Thus, in assessing the possible estrogenic effects of organochlorine compounds, endometrial cancer is a natural focus.

As is the case for breast cancer, international cancer trends are not consistent with an association between organochlorines and endometrial cancer. The incidence of this malignancy is increasing in some populations and decreasing in others.[242,244,296,297] Given the established relationship between postmenopausal estrogen therapy and endometrial cancer, and the relatively brief latency of this tumor, we would expect environmental estrogen exposures to have a rapid impact on endometrial cancer rates. However, over the last 2 decades, there has been relatively little increase in the incidence of endometrial cancer among younger women in the U.S.[242,244] Postmenopausal incidence underwent dramatic increases during the late 1960s, and peaked during the mid-1970s. This epidemic corresponded closely to the use of unopposed estrogen hormone replacement therapy.[298,299] It might be argued, that these increased rates reflect peak usage of DDT in the 1950s; however, endometrial cancer incidence rates fell sharply with the disuse of estrogen therapy. If biologically persistent organochlorines had contributed to the increased endometrial cancer rates, the impact of withdrawing estrogen therapy would have been far less dramatic, and rates would have remained at least somewhat elevated relative to preepidemic rates. Thus the data do not point to any discernible influence of persistent organochlorine chemicals on endometrial cancer.

Ecological evaluations of the relationship between endometrial cancer and organochlorine exposure are faced with the same methodological limitations that attend ecological studies of organochlorines and breast cancer (see "Evidence from Temporal and Ecological Studies"). Only one published ecological study to date has reported data regarding the effect of TCDD exposure on endometrial or uterine cancer incidence and mortality.[246,247] This study used external rates for reference. In the highest exposure area (zone A), the relative risk for all uterine cancers (ICD 9 179 to 182) was 2.6. Based on only two cases, this was not statistically significant. In the "moderately" exposed area (zone B), the relative risk for uterine cancer was 0.4, also nonsignificant and based on two cases. In the least heavily exposed area

(zone R), the endometrial cancer SIR was 50 (based on nine cases for ICD 9 182), a finding of marginal statistical significance. Endometrial cancer mortality was reported only for zone R. Here, the SMR was 552, a statistically significant increase based on four deaths for ICD 9 182.[246] Apparently most of the increased risk was in the period immediately after the accident, raising the possibility that the subjects were diagnosed before the exposure, but died afterward.

2. Epidemiological Data

Epidemiological investigation of the relation between organochlorine exposure and endometrial cancer is not straightforward. The strong estrogen dependence of the malignancy implies that the effects of weak environmental estrogens will best be evaluated only in full knowledge of the hormone use of the subjects or preferably, only among individuals who have never taken exogenous hormones at all. Obesity is another factor that should be taken into account. Also, particularly in the U.S. some women may not be at risk for endometrial cancer because they have undergone a hysterectomy. To deal with these issues, either relevant data must be collected or the assumption needs to be made that hysterectomy prevalence, obesity, and hormone use are independent of organochlorine exposure, a set of assumptions that probably cannot be made with confidence.

Epidemiological data of any sort regarding organochlorine exposure and endometrial cancer risk are scanty. There have been no case-control or cohort studies similar to those reported for breast cancer, and few occupational cohorts have reported any information regarding endometrial cancer after exposure to either TCDD or PCBs. (Detailed descriptions of the occupational cohort studies have been presented in "Evidence from Occupational Studies"). Lynge[268] investigated 1069 women ever employed before 1982 in the chlorophenoxy herbicide industry in Denmark who thus had presumed TCDD exposure. With over 18,000 woman-years of risk between 1947 and 1982, two cases of endometrial cancer were registered in the Danish National Cancer Registry whereas three cases were expected, based on national rates. This SIR of 67 was not significantly different from 100. As was the case for breast cancer, further follow-up (1983 to 1987) of the workers did not include an evaluation of uterine cancer risk. The mortality analyses of Kogevinas et al.[272] included an evaluation of uterine cancer (unspecified type) in a subgroup of 701 female workers with known exposure to phenoxy herbicides; an increased risk was noted (SMR = 192), but it was based on just one observed case.

In the study by Brown,[273] 1318 female capacitor workers in New York and Massachusetts with presumed heavy PCB exposure were evaluated for endometrial cancer mortality.[274] No evidence of an increase was found; the SMR was 59, based on one observed case. Sinks (1994, personal communication), in a reevaluation of uterine cancer mortality among 846 female employees known to have been exposed to PCBs at an electrical capacitor plant, found no deaths from uterine cancer (vs. 0.32 expected). Similarly, Bertazzi et al.[277] reported no uterine cancer deaths (vs. 0.77 expected) among 1556 female workers employed at an electrical capacitor plant.

Collectively, these ecological and epidemiological data are consistent with a possible antiestrogenic effect of dioxins and related compounds leading to a reduced risk of endometrial cancer. However, the small numbers of subjects involved severely hamper the interpretation of the results. Overall, the data are not sufficient to support even a preliminary conclusion regarding an effect of dioxins and related compounds (or other organochlorines) on endometrial cancer.

C. Organochlorines and Endometriosis

Endometriosis is a disease characterized by the migration of endometrial cells and their proliferation in the abdomen, ovaries, fallopian tubes, intestine or bladder, often causing chronic pain, internal bleeding, and infertility. This endometrial tissue continues to respond to ovarian hormones and, therefore, undergoes cyclic menstrual changes with periodic bleeding.[300] It is estimated that more than 5 million women in the U.S. have endometriosis, which translates into a prevalence of 10% among reproductive-age women.[301]

The etiology of endometriosis is not clearly established. An association has been postulated between endometriosis and infertility, but it is difficult to distinguish whether low fertility precedes or follows endometriosis, and no epidemiological study has evaluated whether delayed childbearing is a risk factor for endometriosis.[300] The maintenance of endometrial implants in castrated monkeys is dependent on sex steroids,[302] suggesting that estrogen and/or progesterone may play a role in the development or progression of endometriosis in an animal model. This would imply that exposures that alter endogenous estrogen levels, such as dietary factors or drugs that affect estrogen metabolism, could affect the risk of endometriosis. Recent studies suggest that immune mechanisms may be involved in the disease process.[303-305] Women with endometriosis often have aggressive macrophages secreting cytokines and growth factors that can irritate endometrial cells.

A recent investigation implicated chronic exposure to TCDD in the pathogenesis of endometriosis in rhesus monkeys.[306] Endometriosis develops spontaneously in rhesus monkeys and resembles the human disease both anatomically and clinically. Endometriosis in dioxin-exposed monkeys was first documented 7 years following the termination of dioxin treatment. Rier et al[306] observed a dose-response relationship between levels of dioxin in the diet and the incidence and severity of endometriosis among 20 animals. Endometriosis was present in 71% and 86% of animals treated with 5 and 25 ppt, respectively, during four years, significantly higher than in the control group (33%). Nevertheless, the results are based on only 20 animals and they require confirmation before suggesting external generalizability and extrapolation to humans.

TCDD functions in part as an antiestrogen. If in fact it does play a role in the development of endometriosis it is unlikely to be through an increase in endogenous estrogen levels. It should be noted, however, that the antiestrogenicity of TCDD has not been demonstrated in monkeys. Dioxin modulates numerous steroid receptor systems that affect uterine function, including estrogen receptor, progesterone receptor, EGF receptor, and prolactin receptor, thereby altering tissue-specific responses to hormones.[106,111,307] Several animal studies demonstrated adverse effects of dioxin on female reproductive function, including reduced fertility, an inability to maintain pregnancy for the full gestational period, and direct effects on female gonads.[106,111,308,309] Dioxin, a potent inhibitor of T lymphocyte function, may also disrupt immunocompetence.[309-312] Rier et al.[306] suggest that chronic immunosuppression in combination with hormonal dysregulation may be the mechanism whereby TCDD affects the reproductive tract and facilitates aberrant growth of endometrial tissue.

Although the duration of exposure was only 4 years, the dietary levels used by Rier et al.,[306] 5 and 25 ppt, caused body fat concentrations of TCDD ranging from 100 to 800 ppt. Background concentrations in human fat (e.g. milk fat, serum lipid) may be about 40 to 60 ppt calculated as TEQs taking into account PCDDs, PCDFs and dioxin like

PCBs.[28] Thus, some human populations may have loads of these pollutants in the range affecting monkeys. However, the prevalence of spontaneous endometriosis among TCDD-unexposed monkeys was about 30%, considerably higher than among women, suggesting that rhesus monkeys may be more susceptible to endometriosis than are humans.

Few other studies have addressed the association between organochlorine compounds and endometriosis. A study by Campbell et al.[313] suggested a link between exposure to PCB compounds and endometriosis in rhesus monkeys. German researchers recently reported that women with endometriosis were more likely than healthy controls to have significantly elevated concentrations of PCBs in their blood.[314] In neither of these studies was sufficient detail presented to allow the evaluation of their methodological basis.

To date, no adequate epidemiological study has been conducted to assess chemical exposure history or organochlorine levels in the blood of women with endometriosis.

IV. CONCLUSIONS

Most of the available data regarding the estrogenic effects and potencies of the various organochlorinated compounds are based on either *in vitro* testing or short-term, usually single exposure, tests *in vivo*. Few studies provide information on estrogenic effects under conditions of long-term exposure to low dosages of potentially estrogenic compounds. This is a major drawback because (at least in younger women) the regulation of estrogens involves a complex feed-back system; the impact of a single exposure to a compound with intrinsic estrogenic properties may thus not mimic a real-world situation characterized by continuous exposure to low doses. It is thus not meaningful to convert single-dose exposures into body burden values, something that would be necessary in order to relate the dosing to the human experience. Furthermore, the data on the estrogenic properties or potencies are rarely comparable, due to differences in testing and experimental conditions. In addition, in most cases, data on the purity of the tested compounds are not adequately stated. Due to the wide range of estrogenic potency displayed by the individual compounds (e.g. *o,p'-DDT* vs *p,p'-DDT*), occurrence of important impurities might have a significant influence on the outcome.

Many of the compounds covered in this review are established animal carcinogens and the dominating tumor types in rodents are carcinomas and adenomas of the liver. In theory, these compounds could increase or reduce the risk of estrogen-related cancers and other diseases through nonhormonal mechanisms, but the prevailing hypothesis is that their hormonal actions are the relevant ones for estrogen-related diseases such as breast cancer, endometrial cancer, and endometriosis. Rarely have effects on tumor incidence in estrogen dependent targets been observed in animals, exceptions being TCDD and Aroclor 1260, where such tumors were observed to have a decreased incidence.[103,177] These chlorinated compounds are also in general devoid of any genotoxic actions and are presumed to act as tumor promoters in the animal systems.

The persistent organochlorinated compounds studied in this monograph occur as a background exposure in the general population, in a mixture that is rather similar in composition in different areas of the industrialized world, except when local contamination has occurred. Any possible estrogenic effect must therefore be related to the total impact of this mixture, that is, both the estrogenic and antiestrogenic components. The lack of data comparing their relative estrogenic potency under realistic conditions consequently makes such a determination difficult or even impossible. However, for the

DDT group as well as for PCDD/Fs together with the dioxin-like PCBs it is possible to make some crude comparisons.

The technical DDT used commercially was a mixture of *o,p'*- and *p,p'*-DDT where *o,p'*-DDT was a minor component that also apparently is less persistent than *p,p'*-DDT and its main metabolite *p,p'*-DDE. Consequently, in humans *p,p'*-DDT and *p,p'*-DDE, are most frequently encountered, whereas *o,p'*-DDT is usually not found.

From all the data available on the estrogenic potency of *o,p'*-DDT (although most of the studies were not designed for this purpose), it can be concluded that *o,p'*-DDT is at least 1000 times less potent than 17β-estradiol. In *in vivo* studies, *o,p'*-DDT has shown estrogenic effects at dose levels of ≥25 mg/kg/d. However, in most studies lower dose levels were not studied. *p,p'*-DDT shares some, but not all, the estrogenic effects of *o,p'*-DDT, for example, it has no effect on estrogen receptor binding. Although it is not possible to quantitate reliably differences in potency, *p,p'*-DDT is almost always less potent than *o,p'*-DDT. Based on limited data, it appears that other DDT metabolites show only slight (*o,p'*-DDD, *o,p'*-DDE) or no (*p,p'*-DDD, *p,p'*-DDE, *m,p'*-DDD, DDA) estrogenic effects.

In animal studies "DDT" (purity not specified) and *o,p'*-DDT have been shown to both promote and inhibit tumor growth. In male Sprague-Dawley rats, 500 ppm "DDT" accelerated the growth of 2-acetamidophenanthrene-induced mammary tumors.[203] This concentration in the diet corresponds to approximately 25 mg/kg/d. A "no observed effect level" (NOEL) could not be derived from this study as 500 ppm was the only dose level used. In another study, *o,p'*-DDT dose relatedly promoted the growth of MT2 mammary adenocarcinoma cells injected in ovariectomized Wistar-Furth rats.[71] Both *o,p'*-DDT and 17β-estradiol promoted tumor growth in a similar way (100 µg 17β-estradiol/kg/d; in between 30 and 100 mg *o,p'*-DDT/kg/d on the dose-response curve).

In the epidemiological study by Wolff et al.,[265] blood was sampled from the women during the period 1985 to 1991 and analyzed for DDE (although not stated, probably *p,p'*-DDE) and PCB. The DDE level in the case patients was 11.0 ± 9.1 ng/ml (mean ± SD). The intake of total DDT (of which *p,p'*-DDE constitutes the major part) at that time has been calculated by Vaz[315] based on figures from the U.S. FDA (1990)[316] and been estimated to be in the range 10 to 77 ng/kg/d. Even if intakes during the preceding years had been considerably higher, they were still several orders of magnitude below those (25 to 30,000,000 ng/kg/d) that caused tumor promotion in the animal studies of Scribner and Mottet[203] and Robison et al.[71] However, these animal studies were not designed for quantitative calculations, had no NOEL levels, and furthermore were performed with unspecified DDT and *o,p'*-DDT, respectively. The comparison thus only gives a very rough picture of the dose relations.

Several studies confirm that TCDD elicits a broad spectrum of antiestrogenic responses. The results indicate that TCDD antagonizes estrogen-induced effects at doses or concentrations equal to those of 17β-estradiol. The antiestrogenic effects are mediated through the AhR and there are studies showing that other dioxin-like compounds (PCDDs, PCDFs, dioxin-like PCBs) also cause these effects with relative potencies in accordance with the TEF concept.

There are indications that both TCDD[103] and the PCB mixture Aroclor 1260[177] reduce the spontaneous formation of estrogen-related tumors (e.g., mammary tumors) in rats. The dose of TCDD that was required for this effect was 0.1 µg/kg/d, corresponding to a body burden of 1400 ng/kg body weight. Short-term studies on TCDD exposure to rats and mice indicate a threshold in the dose-response curves for antiestrogenic ef-

fects and the lowest observed effect levels (LOEL) have been in the range 3 to 20 µg/kg body weight. The average human body burden of TEQs in industrialized countries has been estimated to be 5 to 10 ng/kg body weight. Aroclor 1260 caused similar effects in rats at a dose level of 100 ppm in the diet (corresponding to approximately 5 mg/kg/d). Intake figures for PCBs in industrialized countries for the years 1983 to 1990 have been estimated to be in the range 72 to 239 ng/kg/d.[315] However, it should be noted that the congener patterns differ considerably between Aroclor 1260 and the PCB mixtures present in food.

These crude comparisons thus would indicate that there are differences of several orders of magnitude between effect levels in animal bioassays and body burden or intakes in humans. However, there are no data on possible species differences between humans on the one hand and rats and mice on the other.

From the database available at present it is clear that chlorinated organic environmental contaminants are a diverse group of chemicals that do, at certain dose levels, affect steroid hormone systems in several ways. With regard to estrogen-related events, certain compounds act as estrogens and thus may enforce estrogenic activities in the body, whereas others act as antiestrogens and counteract many estrogen-induced activities. The final outcome of the environmental exposure to the various organochlorines will depend on the balance between these actions and the actual exposure levels. At present there are no biological, toxicological or analytical data available that can be utilized to indicate that there would be a net effect one way or the other, or that exposure levels that can affect human health have been achieved in any but the most unusual situations.

The hypothesis that human exposure to environmental levels of organochlorines would favor an estrogenic overactivity leading to an increase in estrogen-dependent formation of mammary tumors is not supported by the existing *in vitro* and animal evidence, but neither can it be rejected on the basis of this evidence alone. However, it is questionable whether the background levels of organochlorines in the general population will be high enough to elicit any of these effects. In fact, the crude comparisons made above would indicate that this is unlikely. Furthermore, this question must also be addressed in relation to the exposure to generally occurring natural estrogenic and antiestrogenic compounds in the food.[317]

Thus, laboratory data do not provide compelling evidence for an organochlorine-dependent estrogen-mediated effect on breast cancer, endometrial cancer, or endometriosis, although they do not exclude the possibility of such an effect. The epidemiological data in this context are no more informative. Because the organochlorines are only weak estrogens or antiestrogens, one has to accommodate much stronger endogenous or exogenous estrogenic stimuli, as well as the possible competition for estrogen receptors. Pregnancy and menopausal estrogen treatment, for example, are likely to have much more pronounced hormonal effects, albeit more time limited. The epidemiological difficulty is then to discern the effects in women of weak, but prolonged, estrogenic or antiestrogenic exposure in the likely presence of intermittent but much stronger endogenous hormonal influences. Moreover, the chemicals considered are all lipid soluble, and reach human tissues predominately through the diet, they will tend to be ingested together, perhaps in certain types of foods. Thus the body burdens of many organochlorines are likely to be intercorrelated, and related as well to other lipid-soluble substances and to diet. This will complicate attempts to disentangle the independent effects, if any, of these exposures.

However, there are some aspects of the study of organochlorine effects that facili-

tate research. In particular, it is possible to quantitate the exposures through blood or fat measurements because of the persistence of most of these compounds in the body. This has enabled breast cancer studies regarding DDT and PCBs to proceed without the need for detailed environmental exposure histories, which may in any case suffer from imprecision and possible lack of validity.

There are very little data regarding the association of organochlorine exposure with endometriosis. Studies on monkeys have suggested that endometriosis may be associated with exposure to the mainly antiestrogenic TCDD[306] and to PCBs, which may be estrogenic, antiestrogenic, or neither.[313] These studies face the problem of species specificity and small numbers (the Rier study was based on 20 monkeys). The results of a study in humans[314] are difficult to interpret.

The data concerning endometrial cancer are also limited. There is no information available regarding the effects of DDT on risk. Only one occupational study[268] and one ecological study[246,247] presented data regarding the possible impact of TCDD exposure on endometrial or uterine cancer, and only three small occupational studies have examined the role of PCBs[273,274] (Sinks 1994, personal communication). In these investigations, occupation or area of residence was used to imply exposure; no blood or tissue measurements were done. Although there is no suggestion of an increased risk after exposure to TCDD or PCBs, the data cannot support firm conclusions. However, it appears unlikely that exposures at levels similar to those investigated have major or even moderate risk implications for endometrial cancer.

More attention has been given to a possible link between organochlorines and breast cancer. We have reviewed seven studies based on occupational exposure, three studies of ecological design, five small studies of formal or informal case-control design, and two major cohorts analyzed through the nested case-control approach. The occupational studies focus on presumed TCDD or PCB exposure, but have involved relatively small numbers of breast cancer cases and could not control for standard breast cancer risk factors[268–270,272–274] (Sinks 1994, personal communication). Overall, these studies do not suggest that there is substantial effect of TCDD or PCB exposure on breast cancer risk.

Ecological evidence is in general difficult to interpret and has mainly been used in epidemiology for hypothesis generation rather than for their formal evaluation. Two of the ecological studies have been interpreted as supporting an association of DDT, α-HCH or γ-HCH[248] or chemical plant-generated pollution[250] with breast cancer risk, whereas a study with a better defined TCDD exposure[246,247] has suggested an inverse association. A recent report by the EPA on the human health effects of dioxin notes the lack of conclusive epidemiological evidence sufficient to link dioxin to human cancers.[318]

The five case-control-like studies were, with one exception,[263] all based on at most 20 cases of breast cancer and so are subject to considerable chance variation. Most of them examined several compounds, thus raising the issue of interpretation of multiple statistical comparisons. One[262] has examined PCB and DDE and was reported as negative; the largest one,[263] examining several organochlorine compounds, was reported as negative with respect to PCBs and DDT/DDE but positive with respect to β-HCH; one[261] has been reported as positive with respect to both PCBs and DDT; a pilot study by Falck et al.[264] showed elevated values of PCBs and *p,p'*-DDE in women with breast cancer; and one study[266] examined several PCB congeners and other organochlorines and has found higher DDE levels in ER-positive breast cancer cases but lower levels in ER-negative cases. Collectively, the studies do not suggest a clear pattern for any particular organochlorine compound.

The two nested case-control analyses of cohort data are larger and better designed studies. In spite of their design similarities, the two studies had different mean exposure levels and durations of follow-up (and therefore latency). One[265] has been interpreted as supporting an association between *p,p'*-DDE, but not PCBs, and breast cancer, whereas the other and larger study[267] has been interpreted as negative with respect to both exposure types.

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REFERENCES

1. **Davis, D. L. Bradlow, H. L., Wolff, M., Woodruff, T., Hoel, D. G., and Anton-Culver, H.,** Medical hypothesis: xenoestrogens as preventable causes of breast cancer, *Environ. Health Perspect.*,101, 372, 1993.
2. **Hunter, D. J. and Kelsey, K. T.,** Pesticide residues and breast cancer: the harvest of a silent spring? (editorial), *J. Natl. Cancer Inst.*, 85, 598, 1993.
3. **Soto, A. M., Chung, K. L, and Sonnenschein, C.,** The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells, *Environ. Health Perspect.*, 102, 380, 1994.
4. **Manske, D. D. and Corneliussen, P. E.,** Pesticide residues in total diet samples (VII), *Pest. Monit. J.*, 8, 110, 1974.
5. **Kutz, F. W., Wood, P. H., and Bottimore, D. P.,** Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue, *Rev. Environ. Contam. Toxicol.*, 120, 1, 1991.
6. **Levine, R.,** Recognized and possible effects of pesticides in humans, in *Handbook of Pesticide Toxicology*, Hayes, W. J. and Laws, E. R., Jr., Eds., 1991, Vol. 1, chap. 7.
7. **Kimbrough, R. D.,** Human health effects of polychlorinated biphenyls (PCBs), and polybrominated biphenyls (PBBs), *Annu. Rev. Pharmacol. Toxicol.*, 27, 87, 1987.
8. **Hodgson, E., Silver, I. S., Butler, L. E., Lawton, M. P. and Levi, P. E.,** Metabolism, in *Handbook of Pesticide Toxicology*, Hayes, W. J. and Laws, E. R., Jr., Eds., 1991, Vol. 1, chap. 3.
9. **Smith, A. G.,** Chlorinated hydrocarbon insecticides, in *Handbook of Pesticide Toxicology*, Hayes, W. J. and Laws, E. R., Jr., Eds., 1991.
10. **Jones, K. C. and Bennett, B. G.,** Human exposure to environmental polychlorinated dibenzo-*p*-dioxins and dibenzofurans: an exposure commitment assessment for 2,3,7,8-TCDD, *Sci. Total Environ.*, 78, 99, 1989.
11. **Jensen, A. A.,** Chemical contaminants in human milk, in *Residue Reviews*, Gunther, F. A. and Gunther, J. D., Eds., Springer-Verlag, New York, 1983, 1.
12. **Okey, A. B., Riddick, D. S., and Harper P. A.,** Molecular biology of the aromatic hydrocarbon (dioxin) receptor, *TIPS*, 15, 226, 1994.
13. **Safe, S.,** Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors, *Crit. Rev. Toxicol.*, 21, 51, 1990.
14. **Ahlborg, U. G., Brouwer A., Fingerhut, M. A., Jacobson, J. L, Jacobson, S. W., Kennedy, S. W., Kettrup, A. A. F., Koeman, J. H., Poiger, H., Rappe, C., Safe, S. H.,**

Seegal, R. F., Tuomisto, J., and van den Berg, M., Impact of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept, *Eur. J. Pharmacol*, 228, 179, 1992.

15. **NATO/CCMS** (North Atlantic Treaty Organization), International toxicity equivalency factor (I-TEF) method of risk assessment for complex mixtures of dioxins and related compounds, *NATO Rep. No. 176*, 1988.
16. **Jensen, A. A.,** Background levels in humans, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, 345.
17. **Graham, M. F., Hileman, F. D., Kirk, J., Wendling, J., and Wilson, J.,** Background human exposure to 2,3,7,8-TCDD, *Chemosphere*, 14, 925, 1985 .
18. **Hutzinger, O., Blumich, M. J., van den Berg, M., and Olie, K.,** Sources and fate of PCDDs and PCDFs: an overview, *Chemosphere*, 14, 581, 1985.
19. **Reggiani, G.,** Acute human exposure to TCDD in Seveso, Italy, *J. Toxicol Environ. Health*, 6, 27, 1980.
20. **Kahn, P. C., Gochfeld, M., Nygren, M., Hansson, M., Rappe, C., Velez, H., Ghent-Guenther, T., and Wilson, W. P.,** Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange-exposed Vietnam veterans and matched controls, *JAMA*, 259, 1661, 1988.
21. **Norén, K.,** Contemporary and retrospective investigations of human milk in the trend studies of organochlorine contaminants in Sweden, *Sci. Total Environ.*, 139/40, 347, 1993.
22. **Rappe, C.,** Recent data on levels of dioxin and related compounds in breast milk in Europe, *WHO EURO working paper*, 1986.
23. **Wolff, M. S.,** Occupational exposure to polychlorinated biphenyls (PCBs), *Environ. Health Perspect.*, 60, 133, 1985.
24. **Silberhorn, E. M., Glavert, H. P., and Robertson, L. W.,** Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs, *Crit. Rev. Toxicol.*, 20, 439, 1990.
25. **Hammond, P. B., Nisbet, I. C. T., Sarofim, A. F., Drury, W. H., and Nelson, N.,** PCBs-environmental impact, *Environ. Res.*, 5, 249, 1972.
26. **Fries, G. P.,** Polychlorinated biphenyl residues in the milk of environmentally and experimentally contaminated cows, *Environ. Health Perspect.*, 10, 55,1972.
27. **Anderson, H. A.,** General population exposure to environmental concentrations of halogenated biphenyls, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, 345.
28. **Ahlborg, U. G., Becking, G. C., Birnbaum, L. S., Brouwer, A., Derks, H. J. G. M., Feeley, M., Golor, G., Hanberg, A., Larsen, J. C., Liem, A. K. D., Safe, S. H., Schlatter, C., Wærn, F., Younes, M., and Yrjänheikki, E.,** Toxic equivalency factors for dioxin-like PCBs, Report on a WHO-ECEH and IPCS consultation, December 1993, *Chemosphere*, 28, 1049, 1994.
29. **Kimbrough, R. D. and Grandjean, P.,** Occupational exposure, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, 485.
30. **Kreiss, K.,** Studies on populations exposed to polychlorinated biphenyls, *Environ. Health Perspect.*, 60, 193, 1985.
31. **Corliss, J.,** News, *J. Natl. Cancer Inst.*, 85, 602, 1993.
32. **WHO**. *Polychlorinated Biphenyls and Terphenyls* (2nd ed.), Environmental Health Criteria 140, World Health Organization, Geneva, 1993.
33. **Mes, J.,** PCBs in human populations, in *PCBs and the Environment*, Waid, J. S., Ed., CRC, Boca Raton, FL, 1991, 39.
34. **Gartrell, M. J., Craun, J. C., Podrebarac, D. S., and Gunderson, E. L.,** Pesticides, selected elements, and other chemicals in adult total diet samples, October 1979-September

1980, *J. Assoc. Off. Anal. Chem.*, 68, 1184, 1985.

35. **Slorach, S. A. and Vaz, R.,** PCB levels in breast milk: data from the UNEP/WHO pilot project on biological monitoring and some other recent studies, *Environ. Health Perspect.*, 60, 121, 1985.

36. **Bergman, Å., Klasson-Wehler, E., and Kuroki, H.,** Selective retention of hydroxylated PCB metabolites in blood, *Environ. Health Perspect.*, 102, 2, 1994.

37. **WHO,** *DDT And Its Derivatives — Environmental Aspects*, World Health Organization, Geneva, 1989.

38. **Roan, C. C.,** They're eating DDT!, *Farm. Chem.*, 133, 44, 1970.

39. **Morgan, D. P. and Roan, C. C.,** Loss of DDT from storage in human body fat, *Nature*, 238, 221, 1972.

40. **Mes, J., Davies, D. J., Doucet, J., Weber, D., and McMullen, E.,** Levels of chlorinated hydrocarbon residues in Canadian human breast milk and their relationship to some characteristics of the donors, *Food Addit. Contam.*, 10 (4), 429, 1993.

41. **Hoffman, W.,** Relation of pesticide concentration in fat to pathological changes in tissue, *Arch. Environ. Health*, 15, 758, 1967.

42. **Casarett, L. J., Fryer, G. C., Yauger, W. L., and Kelmmer, H. W.,** Organochlorined pesticide and polychlorinated biphenyl residues in biopsied human adipose tissue — Hawaii, *Arch. Environ. Health*, 17, 306, 1968.

43. **Davies, J. E., Edmundson, W. F., Macio, A., Barquet, A., and Cassady, J.,** An epidemiologic application of the study of DDE levels in whole blood, *Am. J. Public Health*, 59, 435, 1969.

44. **Davies, J. E., Edmundson, W. F., Raffonelli, A., Cassady, J. C., and Morgade, C.,** The role of social class in human pesticide pollution, *Am. J. Epidemiol.*, 96, 334, 1972.

45. **Kutz, F. W., Ybs, A. R, and Strassman, S. C.,** Racial stratification of organochlorine insecticide residues in human adipose tissue, *J. Occup. Med.*, 19, 619, 1977.

46. **Sandifer, S. H.,** A case-control study of persons with elevated blood levels of dieldrin, *Arch. Environ. Contam. Toxicol.*, 10, 35, 1981.

47. **Walker, K. C., Goette, M. B., and Batchelor, G. S.,** Pesticide residue in foods. Dichlorodiphenyltrichloroethane and dichlorodiphenyldichloroethylene content of prepared meals, *J. Agric. Food Chem.*, 2, 1034, 1954.

48. **Spear, R.,** Recognized and possible exposure to pesticides, in *Handbook of Pesticide Toxicology*, Hayes, W. J. and Laws, E. R., Jr., Eds., 1991, chap. 6.

49. **International Agency for Research on Cancer (IARC),** DDT and associated compounds (review), Monographs on the evaluation of carcinogenic risks to humans, in *Occupational Exposures in Insecticide Application and Some Pesticides*, Vol. 53, IARC, Lyon, France, 1991.

50. **Murphy, R. S., Kutz, F. W., and Strassman, S. C.,** Selected pesticide residues or metabolites in blood and urine specimens from a general population survey, *Environ. Health Perspect.*, 48, 81, 1983.

51. **Howell, D.E.,** A case of DDT in human fat, *Proc. Okla. Acad. Sci.*, 29, 31, 1948.

52. **Kashyap, R., Iyer, L. R., Singh, M. M., and Kashyap, S. K.,** Evaluation of human exposure to the persistent insecticides DDT and HCH in Ahmedabad, India, *J. Anal. Toxicol.*, 17, 211, 1991.

53. **Murphy, R. and Harvey, C.,** Residues and metabolites of selected persistent hydrocarbons in blood specimens from a general population survey, *Environ. Health Perspect.*, 60, 115, 1985.

54. **Kreiss, K., Zack, M. M., Kimbrough, R. D., Needham, L. L., Smrek, A. L., and Jones, B. T.,** Cross-sectional study of a community with exceptional exposure to DDT, *JAMA*, 245, 1926, 1981.

55. **Wassermann, M., Tomatis, L, Wassermann, D., Day, N. E., Groner, Y., Lazarovici, S., and Rosenfeld, D.,** Epidemiology of organochlorine insecticides in the adipose tissue of Israelis, *Pest. Mon. J.*, 8, 1, 1974.

56. **Laug, E. P., Kunze, F. M., and Prickett, C. S.,** Occurrence of DDT in human fat and milk, *Arch. Ind. Hyg. Occup. Med.*, 3, 245, 1951.

57. **WHO,** *Chlordane Health and Safety Guide* (Health and Safety Guide No. 13), World Health Organization, Geneva, 1988.

58. **IARC,** Chlordane and heptachlor (review), Monographs on the evaluation of carcinogenic risks to humans, in *Occupational Exposures in Insecticide Application And Some Pesticides*, Vol. 53, IARC, Lyon, France, 1991, 115.

59. **Kutz, F. W., Sovocool, G. W., Strassman, S., and Lewis, R. G.,** Transnonachlor residues in human adipose tissue, *Bull. Environ. Contam. Toxicol*, 16, 9, 1976.

60. **Savage, E. P., Keefe, T. J., Tessari, J. D., Wheeler H. W., Applehans, F. M., Goes, E. A., and Ford, S. A.,** National study of chlorinated hydrocarbon insecticide residues in human milk, USA, *Am. J. Epidemiol*, 113, 413, 1981.

61. **Kutz, F. W., Strassman, S. C., Stroup, C. R., Carra, J. S., Leininger, C. C., Watts, D. L, and Sparacino, C. M.,** The human body burden of mirex in the Southeastern United States, *J. Toxicol. Environ. Health*, 15, 385, 1985.

62. **Öberg, L. G. and Rappe, C.,** Biochemical formulation of PCDD/Fs from chlorophenols, *Chemosphere*, 25, 49, 1992.

63. **Sundström, G., Jensen, S., Jansson, B., and Erne, K.,** Chlorinated phenoxyacetic acid derivatives and tetrachlorodibenzo-*p*-dioxin in foliage after application of 2,4,5-trichlorophenoxyacetic acid ester, *Arch. Environ. Contam. Toxicol*, 8, 441, 1979.

64. **Welch, R. M., Levin, W., and Conney, A. H.,** Estrogenic action of DDT and its analogs, *Toxicol. Appl. Pharmacol.*, 14, 358, 1969.

65. **Bitman, J. and Cecil, H. C.,** Estrogenic activity of DDT analogs and polychlorinated biphenyls, *J. Agric. Food Chem.*, 18, 1108, 1970.

66. **Kupfer, D.,** Studies on short and long-range estrogenic action of chlorinated hydrocarbon pesticides, *Banbury Report*, 11, 379, 1982.

67. **Nelson, J. A., Struck, R. F., and James, R.,** Estrogenic activities of chlorinated hydrocarbons, *J. Toxicol. Environ. Health*, 4, 325, 1978.

68. **Robison, A. K., Schmidt, W. A., and Stancel, G. M.,** Estrogenic activity of DDT: estrogen-receptor profiles and the responses of individual uterine cell types following *o,p'*-DDT administration, *J. Toxicol. Environ. Health*, 16, 493, 1985.

69. **Galand, P., Mairesse, N., Degraef, C., and Rooryck, J.,** *o,p'*-DDT (1,1,1-trichloro-2(*p*-chlorophenyl) 2-(*o*-chlorophenyl) ethane is a purely estrogenic agonist in the rat uterus in vivo and in vitro, *Biochem. Pharmacol.*, 36, 397, 1987.

70. **Bustos, S., Denegri, J. C., Diaz, F., and Tchernitchin, A. N.,** *p,p'*-DDT is an estrogenic compound, *Bull. Environ. Contam. Toxicol*, 41, 496, 1988.

71. **Robison, A. K., Sirbasu, D. A., and Stancel, G. M.,** DDT supports the growth of an estrogen-responsive tumor, *Toxicol. Lett.*, 27, 109, 1985.

72. **Bulger, W. H. and Kupfer, D.,** Estrogenic action of DDT analogs, *Am. J. Ind. Med.*, 4, 163, 1983.

73. **Faber, K. A., Basham, K., and Hughes, C. L. J.,** The effect of neonatal exposure to DES and *o,p'*-DDT on pituitary responsiveness to GnRH in adult castrated rats, *Reprod. Toxicol.*, 5, 363, 1991.

74. **Uphouse, L. and Williams, J.,** Sexual behavior of intact female rats after treatment with *o,p'*-DDT or *p,p'*-DDT, *Reprod. Toxicol.*, 3, 33, 1989.

75. **Mason, R. R. and Schulte, G. J.,** Estrogen-like effects of *o,p'*-DDT on the progesterone receptor of rat uterine cytosol, *Res. Commun. Chem. Pathol. Pharmacol*, 29, 281, 1980.

76. **Bulger, W. H. and Kupfer, D.,** Effect of xenobiotic estrogens and structurally related compounds on 2-hydroxylation of estradiol and on other monoxygenase activities in rat liver, *Biochem. Pharmacol.*, 32, 1005, 1983.

77. **Forster, M. S., Wilder, E. L., and LeRoy Heinrichs, W.,** Estrogenic behavior of 2(*O*-chlorophenyl)-2-(*P*-chlorophenyl)-1,1,1-trichloroethane and its homologues, *Biochem. Pharmacol.*, 24, 1777, 1975.

78. **Stancel, G. M., Ireland, J. S., Mukku, V. R., and Robison, A. K.,** The estrogenic activity of DDT: in vivo and in vitro induction of a specific estrogen inducible uterine protein by *o,p'*-DDT, *Life Sci*, 27, 1111, 1980.

79. **Mason, R. R., and Schulte, G. J.,** Interaction of *o,p'*-DDT with the estrogen-binding protein (EBP) of DMBA-induced rat mammary tumors, *Res. Commun. Chem. Pathol. Pharmacol.*, 33, 119, 1981.

80. **Robison, A. K., Mukku, V. R., Spalding, D. M., and Stancel, G. M.,** The estrogenic activity of DDT: the in vitro induction of an estrogen-inducible protein by *o,p'*-DDT, *Toxicol. Appl. Pharmacol.*, 76, 537, 1984.

81. **McBlain, W. A.,** The levo enantiomer of *o,p'*-DDT inhibits the binding of 17β-estradiol to the estrogen receptor, *Life Sci.*, 40, 215, 1987.

82. **Robison, A. K., and Stancel, G. M.,** The estrogenic activity of DDT: correlation of estrogenic effect with nuclear level of estrogen receptor, *Life Sci.*, 31, 2479, 1982.

83. **Etgen, A. M.,** 1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)2,2,2-trichloroethane: a probe for studying estrogen and progestin receptor mediation of female sexual behavior and neuroendocrine responses, Endocrinology, 111, 1498, 1982.

84. **Bitman, J., Cecil, H. C., Harris, S. J., and Feil, V. J.,** Estrogenic activity of *o,p'*-DDT metabolites and related compounds, *J. Agric. Food Chem.*, 26, 149, 1978.

85. **Johnson, D. C., Kogo, H., and Dey, S. K.,** Multiple estrogenic action of *o,p'*-DDT: initiation and maintenance of pregnancy in the rat, *Toxicology*, 53, 79, 1988.

86. **Johnson, D. C., Sen, M., and Dey, S. K.,** Differential effects of dichlorodiphenyltrichloroethane analogs, chlordecone, and 2,3-7,8-tetrachlorodibenzo-*p*-dioxin on establishment of pregnancy in the hypophysectomized rat, *Proc. Soc. Exp. Biol. Med.*, 199, 42, 1992.

87. **Bulger, W. H., Muccitelli, R. M., and Kupfer, D.,** Studies on the in vivo and in vitro estrogenic activities of methoxychlor and its metabolites. Role of hepatic monooxygenase in methoxychlor activation, *Biochem. Pharmacol.*, 27, 2417, 1978.

88. **Ousterhout, J., Struck, R. F., and Nelson, J. A.,** Estrogenic activities of methoxychlor metabolites, *Biochem. Pharmacol.*, 30, 2869, 1981.

89. **Williams, J., Eckols, K., and Uphouse, L.,** Estradiol and chlorodecone interactions with the estradiol receptor, *Toxicol. Appl. Pharmacol.*, 98, 413, 1989.

90. **Hammond, P. B., Katzenellenbogen, B. S., Krauthammer, N., and McConnell, J.,** Estrogenic activity of the insecticide chlordecone (Kepone) and interaction with uterine estrogen receptors, *Proc. Natl. Acad. Sci. USA*, 76, 6641, 1979.

91. **Cochran, R. C. and Wiedow, M. A.,** Chlordecone lacks estrogenic properties in the male rat, *Toxicol. Appl. Pharmacol.*, 76, 519, 1984.

92. **Foster, W. G., McMahon, A., Villeneuve, D. C., and Jarrel, J. F.,** Hexachlorobenzene (HCB) suppresses circulating progesterone concentrations during the luteal phase in the cynomolgus monkey, *J. Appl. Toxicol.*, 12, 13, 1992.

93. **Foster, W. G., Pentick, J. A., McMahon, A., and Lecavalier P. R.,** Ovarian toxicity of hexachlorobenzene (HCB) in the superovulated female rat, *J. Biochem. Toxicol.*, 7, 1, 1992.

94. **McKinney, J. D. and Waller, C. L.,** Polychlorinated biphenyls as hormonally active structural analogues, *Environ. Health Perspect.*, 102, 290, 1994.

95. **Jansen, H. T., Cooke, P. S., Porcelli, J., Liu, T. C., and Hansen, L. G.,** Estrogenic and antiestrogenic actions of PCBs in the female rat: in vitro and in vivo studies, *Reprod. Toxicol.*, 7, 237, 1993.

96. **Ecobichon, D. J. and MacKenzie, D. O.,** The uterotropic activity of commercial and isomerically pure chlorobiphenyls in the rat, *Res. Commun. Chem. Pathol. Pharmacol.*, 9, 85, 1974.

97. **Korach, K. S., Sarver, P., Chae, K., McLachlan, J. A., and McKinney, J. D.,** Estrogen receptor-binding activity of poly-

chlorinated hydroxybiphenyls: conformationally restricted structural probes, *Mol. Pharmacol.*, 33, 120, 1988.

98. **Müller, W. F., Hobson, W., Fuller, G. B., Knauf, W., Coulston, F., and Korte, F.,** Endocrine effects of chlorinated hydrocarbons in rhesus monkeys, *Ecotoxicol. Environ. Safety*, 2, 161, 1978.

99. **Truelove, J. F., Tanner, J. R., Langlois, I. A., Stapley R. A., Arnold, D. L., and Mes, J. C.,** Effect of polychlorinated biphenyls on several endocrine reproductive parameters in the female rhesus monkey, *Arch. Environ. Contam. Toxicol.*, 19, 939, 1990.

100. **Gellert, R. J.,** Uterotrophic activity of polychlorinated biphenyls (PCB) and induction of precocious reproductive aging in neonatally treated female rats, *Environ. Res.*, 16, 123, 1978.

101. **Vincent, D. R., Bradshaw, W. S., Booth, G. M., Seegmiller R. E., and Allen, S. D.,** Effect of PCB and DES on rat monoamine oxidase, acetylcholinesterase, testosterone, and estradiol ontogeny, *Bull. Environ. Contam. Toxicol.*, 48, 884, 1992.

102. **Lundkvist, U. and Kindahl, H.,** Plasma concentrations of 15-keto-13,14-dihydro-PGF-2α, oestrone sulphate, oestradiol-17β and progesterone in pregnant guinea-pigs treated with polychlorinated biphenyls, *J. Reprod. Fertil.*, 87, 55, 1989.

103. **Kociba, R. J., Keyes, D. G., Beyer, J. E., Carreon, R. M., Wade, C. E., Dittenber, D. A., Kalnins, R. P., Frauson, L. E., Park, C. N., Barnard, S. D., Hummel, R. A., and Humiston, C. G.,** Results of a two-year toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rats, *Toxicol. Appl. Pharmacol.*, 46, 279, 1978.

104. **Gierthy, J. F., Bennett, J. A., Bradley, L. M., and Cutler, D. S.,** Correlation of in vitro and in vivo growth suppression of MCF-7 human breast cancer by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Cancer Res.*, 53, 3149, 1993.

105. **Holcomb, M. and Safe, S.,** Inhibition of 7,12-dimethylbenzanthracene-induced rat mammary tumor growth by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Cancer Lett.*, 82, 43, 1994.

106. **Safe, S., Harris, M., Biegel, L, and Zacharewski, T.,** Mechanism of action of TCDD as an antiestrogen in transformed human breast cancer and rodent cell lines, in *Banbury Report 35. Biological Basis for Risk Assessment of Dioxins and Related Compounds*, Gallo, M. J., Scheuplein, R. J., and van der Heijden, K. A., Eds, Cold Spring Harbor Laboratory Press, New York, 1991, 367.

107. **Astroff, B. and Safe, S.,** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin as an antiestrogen: effect on rat uterine peroxidase activity, *Biochem. Pharmacol.*, 39, 485, 1990.

108. **Astroff, B., Rowlands, C., Dickerson, R., and Safe, S.,** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin inhibition of 17β-estradiol-induced-increases in rat uterine epidermal growth factor receptor binding activity and gene expression, *Mol. Cell. Endocrinol.*, 72, 247, 1990.

109. **Astroff, B., Eldridge, B., and Safe, S.,** Inhibition of the 17β-estradiol-induced and constitutive expression of the cellular proto-oncogene c-fos by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the female rat uterus, *Toxicol. Lett.*, 56, 305, 1991.

110. **Gallo, M. A., Hesse, E. J., MacDonald, G. J., and Umbreit, T. H.,** Interactive effects of estradiol and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on hepatic-cytochrome P-450 and mouse uterus, *Toxicol Lett.*, 32, 123, 1986.

111. **Safe, S., Astroff, B., Harris, M., Zacharewski, T., Dickerson, R., Romkes, M., and Biegel, L.,** 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds as antiestrogens: characterization and mechanism of action, *Pharmacol. Toxicol.*, 69, 400, 1991.

112. **Goldstein, J. A., Lin, F. H., Stohs, S. J., Graham, M., Clarke, G., Birnbaum, L., and Lucier, G.,** The effects of TCDD on receptors for epidermal growth factor, glucocorticoid, and estrogen in Ah-responsive and Ah-nonresponsive congenic mice and the effects of TCDD on estradiol metabolism in a liver tumor promotion model in female rats, *Mouse Liver Carcinog.*, 331, 187, 1990.

113. **Lin, F. H., Stohs, S. J., Birnbaum, L. S., Clark, G., Lucier, G. W., and Goldstein,**

J. A., The effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on the hepatic estrogen and glucocorticoid receptors in congenic strains of Ah responsive and Ah nonresponsive C57BL/6J mice, *Toxicol. Appl. Pharmacol.*, 108, 129, 1991.

114. **DeVito, M. J., Thomas, T., Martin, E., Umbreit, T. H., and Gallo, M. A.,** Antiestrogenic action of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: tissue-specific regulation of estrogen receptor in CD1 mice, *Toxicol. Appl. Pharmacol.*, 113, 284, 1992.

115. **Shiverick, K. T. and Muther, T. F.,** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) effects on hepatic microsomal steroid metabolism and serum estradiol of pregnant rats, *Biochem. Pharmacol.*, 32, 991, 1983.

116. **Gray, L. E., Ostby, J. S., Kelce, W., Marshall, R., Diliberto, J. J., and Birnbaum, L. S.,** Perinatal TCDD exposure alters sex differentiation in both female and male LE hooded rats, in *13th International Symposium on Chlorinated Dioxins and Related Compounds*, Vienna, 13, 337, 1993.

117. **Bookstaff, R. C., Moore, R. W., and Peterson, R. E.,** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin increases the potency of androgens and estrogens as feedback inhibitors of luteinizing hormone secretion in male rats, *Toxicol. Appl. Pharmacol.*, 104, 212, 1990.

118. **Moore, R. W., Bookstaff, R. C., Mably, T. A., and Peterson, R. E.,** Differential effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on responsiveness of male rats to androgens, 17β-estradiol, luteinizing hormone, gonadotropin-releasing hormone and progesterone; *Chemosphere*, 25, 91, 1992.

119. **Hruska, R. E., and Olson, J. R.,** Species differences in estrogen receptors and in the response to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure, *Toxicol. Lett.*, 48, 289, 1989.

120. **Romkes, M., Piskorska-Pliszczynska, J., and Safe, S.,** Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on hepatic and uterine estrogen receptor levels in rats, *Toxicol. Appl. Pharmacol.*, 87, 306, 1987.

121. **Romkes, M., Piskorska-Pliszczynska, J., and Safe, S.,** Role of the Ah receptor in mediating the down regulation of uterine and hepatic estrogen receptor levels in rats, *Chemosphere*, 16, 1691, 1987.

122. **Astroff, B. and Safe, S.,** Comparative antiestrogenic activities of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and 6-methyl-1,3,8-trichlorodibenzofuran in female rat, *Toxicol. Appl. Pharmacol.*, 95, 43, 1988.

123. **Astroff, B., Romkes, M., and Safe, S.,** Mechanism of action of 2,3,7,8-TCDD and 6-methyl-1,3,8-trichlorodibenzofuran (MCDF) as antiestrogens in the female rat, *Chemosphere*, 19, 785, 1989.

124. **Astroff, B. and Safe, S.,** 6-Alkyl-1,3,8-trichlorodibenzofurans as antiestrogens in female Sprague-Dawley rats, *Toxicology*, 69, 187, 1991.

125. **Dickerson, R., Howie, L., and Safe, S.,** The effect of 6-nitro-1,3,8-trichlorodibenzofuran as a partial estrogen in the female rat uterus, *Toxicol. Appl. Pharmacol*, 113, 55, 1992.

126. **Chadwick, R. W., Cooper, R. L., Chang, J., Rehnberg, G. L., and McElroy, W. K.,** Possible antiestrogenic activity of lindane in female rats, *J. Biochem. Toxicol*, 3, 147, 1988.

127. **Wang, X., Porter, W., Krishnan, V., Narasimhan, T. R., and Safe, S.,** Mechanism of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)-mediated decrease of the nuclear estrogen receptor in MCF-7 human breast cancer cells, *Mol. Cell. Endocrinol*, 96, 159, 1993.

128. **Biegel, L. and Safe, S.,** Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on cell growth and the secretion of the estrogen-induced 34-, 52-, and 160-kDa proteins in human breast cancer cells, *J. Steroid Biochem. Mol. Biol.*, 37, 725, 1990.

129. **Krishnan, V., Narisimhan, T. R., and Safe, S.,** Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as an antiestrogen in MCF-7-human breast cancer cells, *Chemosphere*, 25, 947, 1992.

130. **Safe, S., Biegel, L., Harris, M., Narasimhan, T. R., Lui, H., and Fernandez, P.,** Inhibition of estrogen-and growth factor-induced proliferation of human breast cancer cell lines by TCDD: characterization and mechanistic studies, *Chemosphere*, 25, 83, 1992.

131. **Krishnan, V. and Safe, S.,** Antiestrogenic activity of polychlorinated biphenyl (PCB) *congeners and mixtures in MCF-7 human* breast cancer cells, *Toxicologist*, 12, 32, 1992.

132. **Chaloupka, K., Krishnan, V., and Safe, S.,** Polynuclear aromatic hydrocarbon carcinogens as antiestrogens in MCF-7 human breast cancer cells: role of the Ah receptor, *Carcinogenesis*, 13, 2233, 1992.

133. **Gierthy, J. F., Lincoln, D. W., Gillespie, M. B., Seeger, J. L, Martinez, H. L., Dickerman, H. W., and Kumar, S. A.,** Suppression of estrogen-regulated extracellular plasminogen activator activity of MCF-7 cells by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Cancer Res.*, 47, 6198, 1988.

134. **Liu, H., Biegel, L., Narasimhan, T. R., Rowlands, C., and Safe, S.,** Inhibition of insulin-like growth factor-I responses in MCF-7 cells by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds, *Mol. Cell. Endocrinol.*, 87, 19, 1992.

135. **Krishnan, V. and Safe, S.,** Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: quantitative structure-activity relationships, *Toxicol. Appl. Pharmacol.*, 120, 55, 1993.

136. **Zacharewski, T., Harris, M., Biegel, L., Morrison, V., Merchant, M., and Safe, S.,** 6-Methyl-1,3,8-trichlorodibenzofuran (MCDF) as an antiestrogen in human and rodent cancer cell lines: evidence for the role of the Ah receptor, *Toxicol. Appl. Pharmacol.*, 113, 311, 1992.

137. **Narasimhan, T. R., Safe, S., Williams, H. J., and Scott, A. I.,** Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on 17β-estradiol-induced glucose metabolism in MCF-7 human breast cancer cells ^{13}C Nuclear magnetic resonance spectroscopy studies, *Mol. Pharmacol.*, 40, 1029, 1991.

138. **Gierthy, J. F. and Lincoln II, D. W.,** Inhibition of postconfluent focus production in cultures of MCF-7 human breast cancer cells by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Breast Cancer Res. Treat.*, 12, 227, 1988.

139. **Harris, M., Zacharewski, T., and Safe, S.,** Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds on the occupied nuclear estrogen receptor in MCF-7 human breast cancer cells, *Cancer Res.*, 50, 3579, 1990.

140. **Zacharewski, T., Harris, M., and Safe, S.,** Evidence for the mechanism of action of the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-mediated decrease of nuclear-estrogen receptor levels in wild-type and mutant mouse hepa lclc7 cells, *Biochem. Pharmacol.*, 41, 1931, 1991.

141. **Graham, M. J., Lucier, G. W., Linko, P., Maronpot, R. R., and Goldstein, J. A.,** Increases in cytochrome P-450 mediated 17β-estradiol 2-hydroxylase activity in rat liver microsomes after both acute administration and subchronic administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in a two-stage hepatocarcinogenesis model, *Carcinogenesis*, 9, 1935, 1988.

142. **Goldstein, J. A., Graham, M. J., Sloop, T., Maronpot, R., Goodrow, T., and Lucier, G. W.,** Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on estradiol metabolism and enzyme-altered foci in a two stage hepatocarcinogenesis model in rats, *Chemosphere*, 18, 695, 1989.

143. **Gierthy, J. F., Lincoln II, D. W., Kampcik, S. J., Dickerman, H. W., Bradlow, H. L., Niwa, T., and Swaneck, G. E.,** Enhancement of 2 and 16α-estradiol hydroxylation in MCF-7 human breast cancer cells by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Biochem. Biophys. Res. Commun.*, 157, 515, 1988.

144. **Spink, D. C., Lincoln, D. W., Dickerman, H. W., and Gierthy, J. F.,** 2,3,7,8-tetrachlorodibenzo-*p*-dioxin causes an extensive alteration of 17β-estradiol metabolism in MCF-7 breast tumor cells, *Proc. Natl. Acad. Sci.* U.S.A., 87, 6917, 1990.

145. **Spink, D. C., Lincoln, D. W., II, Johnson, J. A., Dickerman, H. W., and Gierthy, J. F.,** Stimulation of 17β-estradiol metabolism in MCF-7 breast cancer cells by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Chemosphere*, 25, 87, 1992.

146. **Spink, D. C., Eugster, H-P., Lincoln, D. W., Schuetz, J. D., Schuetz, E. G., Johnson, J. A., Kaminsky, L. S., and Gierthy, J. F.,** 17β-Estradiol hydroxylation catalyzed by human cytochrome P450 1A1: a comparison

of the activities induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in MCF-7 cells with those from heterologous expression of the cDNA, *Arch. Biochem. Biophys.*, 293, 342, 1992.

147. **DeVito, M. J., Ma, X. F., Babish, J. G., Menache, M., and Birnbaum, L. S.,** Dose-response relationships in mice following subchronic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: CYP1A1, CYP1A2, estrogen receptor, and protein tyrosine phosphorylation, *Toxicol. Appl. Pharmacol.*, 124, 82, 1994.

148. **Romkes, M. and Safe, S.,** Comparative activities of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on hepatic and uterine estrogen receptor levels in rats, *Toxicol. Appl. Pharmacol.*, 87, 306, 1988.

149. **Romkes, M. and Safe, S.,** Comparative effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and progesterone on estrogenic responses in rats, *Chemosphere*, 18, 745, 1989.

150. **DeVito, M., Umbreit, T. H., Thomas, T., and Gallo, M. A.,** An analogy between the actions of the Ah receptor and the estrogen receptor for use in the biological basis for risk assessment of dioxin, in *Banbury Report 35. Biological Basis for Risk Assessment of Dioxins and Related Compounds*, Gallo, M. A., Scheuplein R. J., and van der Heijden, K. A., Eds., Cold Spring Harbor Laboratory Press, New York, 1991, 427.

151. **White, T. E. K. and Gasiewicz, T. A.,** The human estrogen receptor structural gene contains a DNA sequence that binds activated mouse and human Ah receptors: a possible mechanism of estrogen receptor regulation by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Biochem. Biophys. Res. Commun.*, 193, 956, 1993.

152. **Demirpence, E., Balaguer, P., Trousse, F., Nicolas, J. C., Pons, M., and Gagne, D.,** Antiestrogenic effects of all-trans-retinoic acid and 1,25-dihydroxyvitamin D3 in breast cancer cells occur at the estrogen response element level but through different molecular mechanisms, *Cancer Res.*, 54, 1458, 1994.

153. **Poland, A. and Glover, E.,** Chlorinated biphenyl induction of aryl hydrocarbon hydroxylase activity: a study of structure activity relationship, *Mol. Pharmacol.*, 13, 924, 1977.

154. **Sawyer, T. and Safe, S.,** PCB isomers and congeners: induction of aryl hydrocarbon hydroxylase and ethoxyresorufin *O*-deethylase enzyme activities in rat hepatoma cells, *Toxicol. Lett.*, 13, 87, 1982.

155. **International Agency for Research on Cancer (IARC),** *Monographs on the evaluation of carcinogenic risks to humans*, Overall evaluations of carcinogenicity: an updating of IARC Monographs Vol. 1 to 42 (Suppl. 7), 1987.

156. **Agency for Toxic Substances and Disease Registry (ATSDR),** *Toxicological Profile for Methoxychlor*, U.S. Department of Health and Human Services, TP-93/11, 1994.

157. **International Programme on Chemical Safety (IPCS),** *Mirex*, Environmental Health Criteria 44, World Health Organization, Geneva, 1984.

158. **International Programme on Chemical Safety (IPCS),** *Chlordecone*, Environmental Health Criteria 43, World Health Organization, Geneva, 1984.

159. **Poland, A. and Knutson, J. C.,** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity, *Annu. Rev. Pharmacol. Toxicol.*, 22, 517, 1982.

160. **Safe, S. H.,** Comparative toxicology and mechanism of action of polychlorinated dibenzo-*p*-dioxins and dibenzofurans, *Annu. Rev. Pharmacol. Toxicol.*, 26, 371, 1986.

161. **Goldstein, J. A. and Safe, S.,** Mechanism of action and structure-activity relationship for the chlorinated dibenzo-*p*-dioxins and related compounds, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, 239.

162. **Kociba, R. J.,** Summary and critique of rodent carcinogenicity studies of chlorinated dibenzo-*p*-dioxins, in *Public Health Risks of the Dioxins*, Lowrance, W. W., Ed., Rockefeller University, New York, 1984, 77.

163. **Kimbrough, R. D., Buckley, J., Fishbein, L., Flamm, G., Kasza, L., Marcus, W., Shibko, S., and Teske, R.,** Animal toxicology, *Environ. Health Perspect.*, 24, 173, 1978.

164. **Van Miller, J. P., LaLich, J. J., and Allen, J. R.,** Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Chemosphere*, 9, 537, 1977.

165. **National Toxicology Program (NTP),** Bioassay of 1,2,3,6,7,8- and 1,2,3,7,8,9-Hexachlorodibenzo-*p*-Dioxin for Possible Carcinogenicity, DHHS Publication (NIH) 80–1754, National Toxicology Program, Research Triangle Park, NC, 1980.

166. **National Toxicology Program (NTP),** Bioassay of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin for Possible Carcinogenicity, NTP-TR-201/209, DHHS Publication (NIH) 82-1765, National Toxicology Program, Research Triangle Park, NC, 1982.

167. **Rao, M. S., Subbarao, V., Prasad, J. D., and Scarpelli, D. G.,** Carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the Syrian golden hamster, *Carcinogenesis*, 9, 1677, 1988.

168. **U.S. EPA,** Health Assessment Document for Polychlorinated Dibenzo-*p*-Dioxins, EPA/600/8-84/014F, Office of Health and Environmental Assessment, Washington, D.C., 1985.

169. **Nessel, C. S. and Gallo, M. A.,** Dioxins and related compounds, in *Environmental Toxicants: Human Exposures and Their Health Effects*, Lippmann, M. Ed., Van Nostrand Reinhold, New York, 1992, 163.

170. **Kimbrough, R. D.,** Laboratory and human studies on polychlorinated biphenyls (PCBs) and related compounds, *Environ. Health Perspect.*, 59, 99, 1985.

171. **Shu, H. P., Paustenbach, D. J., and Murray, F. J.,** A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor-promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Regul. Toxicol. Pharmacol.*, 7, 57, 1987.

172. **Gold, L. S., Slone, T. H., Stern, B. R., Manley, N. B., and Ames, B.,** Rodent carcinogens: setting priorities, *Science*, 258, 261, 1992.

173. **McConnell, E. E.,** Acute and chronic toxicity and carcinogenesis in animals, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, 161.

174. **Ito, N., Nagasaki, H., Arai, M., Makiura, S., Sugihara, S., and Hirao, K.,** Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride, *J. Natl. Cancer Inst.*, 51, 1637, 1973.

175. **Kimura, N. T. and Baba, T.,** Neoplastic changes in the rat liver induced by polychlorinated biphenyls, *Gann.*, 64, 105, 1973.

176. **Kimbrough, R. D. and Linder, R. E.,** Induction of adenofibrosis and hepatomas of the liver in BALB/cJ mice by polychlorinated biphenyls (Arochlor 1254), *J. Natl. Cancer Inst.*, 53, 547, 1974.

177. **Kimbrough, R. D., Squire, R. A., Linder, R. E., Strandberg, J. D., Montali, R. J., and Burse, V. W.,** Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Arochlor 1260, *J. Natl. Cancer Inst.*, 55, 1453, 1975.

178. **U.S. National Cancer Institute,** Bioassay of Aroclor 1254 for Possible Carcinogenicity, (Carcinogenesis Technical report serial number 38), DHEW Publication number (NIH) 78–838, U.S. Department of Health, Education, and Welfare, National Institutes of Health, Bethesda, MD, 1977.

179. **Norback, D. H. and Weltman, R. H.,** Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat, *Environ. Health Perspect.*, 60, 97, 1985.

180. **Morgan, R. W., Ward, J. M., and Hartman, P. E.,** Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats, *Cancer Res.*, 41, 5052, 1981.

181. **Ward, J. M.,** Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254, *Environ. Health Perspect.*, 60, 89, 1985.

182. **U.S. National Cancer Institute,** Bioassays of DDT, TDE, and *p,p'*-DDE for Possible Carcinogenicity, (Tech. Rep. No. 131; PB-